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Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration
The STAIRWAY Phase 2 Randomized Clinical Trial

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IMPORTANCE Faricimab neutralizes angiopoietin-2 and vascular endothelial growth factor A via both simultaneous and independent binding.

OBJECTIVE To evaluate extended dosing with faricimab, the first bispecific antibody designed for intraocular use, in patients with neovascular age-related macular degeneration.

DESIGN, SETTING, AND PARTICIPANTS This phase 2 randomized clinical trial was a 52-week multicenter, active comparator–controlled, parallel-group study. Study participants were enrolled in 25 sites in the US from January and March 2017 with treatment-naive choroidal neovascularization secondary to neovascular age-related macular degeneration and best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study letter score of 73 (approximate Snellen equivalent, 20/40) to 24 (approximate Snellen equivalent, 20/320). Analysis began January 2017 and ended March 2018.

INTERVENTIONS Participants were randomized 1:2:2 to receive intravitreal ranibizumab, 0.5 mg, every 4 weeks or faricimab, 6.0 mg, every 12 or 16 weeks. Participants in the faricimab arms initially received 4 monthly injections of faricimab. No rescue injections were allowed. Participants randomized to dosing every 16 weeks were assessed for disease activity at week 24 using prespecified criteria. Those with no active disease continued dosing every 16 weeks through trial end; participants with disease activity continued received dosing every 12 weeks.

MAIN OUTCOMES AND MEASURES Mean change in BCVA from baseline at week 40.

RESULTS Of 76 participants enrolled (mean [SD] age, 78.5 [8.5] years; age range, 56-94 years; 41 women [58%]; 69 white [97%]), 16 (21.0%) were randomized to ranibizumab every 4 weeks, 29 (38.2%) to faricimab every 12 weeks, and 31 (40.8%) to faricimab every 16 weeks. At week 24, 12 weeks after their last initiation injection, 65% (36 of 55) of all faricimab-treated participants had no disease activity. At week 40, adjusted mean BCVA gains from baseline (Early Treatment Diabetic Retinopathy Study letters) were +11.4 (80% CI, 7.8-15.0), +9.3 (80% CI, 6.4-12.3), and +12.5 (80% CI, 9.9-15.1) for the ranibizumab every 4 weeks, faricimab every 12 weeks, and faricimab every 16 weeks arms, respectively. Participants received a mean (SD) total of 12.9 (0.25), 6.7 (0.91), and 6.2 (0.93) injections, for the ranibizumab every 4 weeks, faricimab every 12 weeks, and faricimab every 16 weeks arms, respectively, through week 52. The secondary BCVA and anatomical imaging end points supported the primary end point and were comparable with ranibizumab every 4 weeks. No new or unexpected safety signals were identified.

CONCLUSIONS AND RELEVANCE At week 52, faricimab dosing every 16 weeks and every 12 weeks resulted in maintenance of initial vision and anatomic improvements comparable with monthly ranibizumab. These results suggest a role for simultaneous neutralization of angiopoietin-2 and vascular endothelial growth factor A in providing sustained efficacy through extended durability, warranting further investigation.

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Invited Commentary page 972

Video and Supplemental content

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For more than a decade, intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has been first line in treating neovascular age-related macular degeneration (nAMD).[1-3] However, patients require frequent anti-VEGF injections to maintain visual outcomes.[3-5] Real-world outcome studies show that patients in clinical practice receive fewer injections than patients in randomized clinical trials, correlating with significant vision loss over time.[6-9] Frequent office visits and injections required to maintain vision gains place a significant treatment burden on patients, caregivers, health care professionals, and health care systems.[10-13]

Faricimab, the first bispecific antibody designed for intraocular use, both simultaneously and independently binds and neutralizes angiopoietin (Ang)-2 and VEGF-A with high specificity and potency.[14,15] The fragment crystallizable portion was specifically engineered to reduce systemic exposure and potential for inflammatory adverse events.[14-16] Ang-1/tyrosine kinase with immunoglobulinlike domains 2 signaling maintains stable vasculature and homeostasis; however, Ang-2 blocks Ang-1-mediated activation of tyrosine kinase with immunoglobulinlike domains 2, causing inflammation and vascular destabilization, including leakage and neovascularization.[17,18] Simultaneous Ang-2 and VEGF neutralization has additive benefits in preclinical models of choroidal neovascularization (CNV).[14,15,19] In patients with nAMD, the anti-inflammatory, antipermeability, antiangiogenic, and vascular stabilization effects of Ang-2 neutralization in addition to VEGF-A neutralization are hypothesized to contribute to a sustained effect on efficacy as a consequence of extended durability.

Faricimab was evaluated in the AVENUE (NCT02484690) and BOULEVARD (NCT02699450) phase 2 clinical trials for patients with nAMD and diabetic macular edema, respectively. AVENUE established that safety and efficacy of faricimab in nAMD at fixed dosing intervals every 4 weeks or every 8 weeks was comparable with monthly ranibizumab.[16] BOULEVARD demonstrated improved visual acuity using faricimab compared with ranibizumab in treatment-naive patients with diabetic macular edema and potential for sustained efficacy because patients treated with faricimab went longer before meeting disease reactivation criteria in the off-treatment observation period.[20] The present study, STAIRWAY, was designed to evaluate faricimab at dosing intervals every 16 weeks and every 12 weeks to address the unmet need for sustained efficacy through extended durability in nAMD. The 40- and 52-week outcomes from the STAIRWAY phase 2 trial are reported herein.

Key Points

Question How does extended dosing with faricimab compare with monthly ranibizumab in treating patients with neovascular age-related macular degeneration?

Findings In this phase 2 randomized clinical trial of faricimab in 76 patients, vision gains from baseline were +9.6, +10.1, and +11.4 letters for the monthly ranibizumab, faricimab every-12-weeks, and faricimab every-16-weeks arms, respectively, at week 52.

Meaning Through simultaneous neutralization of angiopoietin-2 and vascular endothelial growth factor A, faricimab maintains initial vision and anatomic improvements comparable with ranibizumab in neovascular age-related macular degeneration; the findings support pursuing extended interval dosing with faricimab in phase 3 trials as a potential alternative to more frequently dosed anti–vascular endothelial growth factor therapy.

Methods

STAIRWAY was a phase 2, multicenter, randomized, active comparator–controlled, participant- and outcome-assessor masked, parallel-group, 52-week clinical trial conducted at 25 sites in the United States between January and March 2017. 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 were reimbursed travel-related expenses. The study protocol and payment schedule were approved by institutional review boards (the full list of 25 sites is in Supplement 1) before study start. The study adhered to the tenets of the Declaration of Helsinki[21] and was conducted in accordance with Good Clinical Practice (GCP; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6)[22]; applicable US Food and Drug Administration regulations; applicable local, state, and federal laws; and the Health Insurance Portability and Accountability Act. The trial protocol is available in Supplement 1.

Study Population

Eligible participants were 50 years or older with treatment-naive subfoveal or juxtafoveal CNV (with a subfoveal component related to the CNV activity) secondary to nAMD and best-corrected visual acuity (BCVA) Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 to 24 (20/40-20/320 Snellen equivalent). Only 1 eye was selected as the study eye; if the intended study eye was ineligible, rescreening was allowed to determine if the other eye would be eligible. Key study eye inclusion criteria were by fluorescein angiography (FA) (CNV lesion total size 6 disc areas or less, CNV component area at least 50% of total lesion size, and active CNV confirmed) and by spectral-domain optical coherence tomography (SD-OCT) (fluid presence by CNV exudation confirmed). Key ocular exclusion criteria were CNV owing to causes besides AMD and any prior or concomitant treatment for CNV, including but not limited to intravitreal treatment, laser photocoagulation, and verteporfin photodynamic therapy. Full inclusion and exclusion criteria are provided in eTable 1 in Supplement 2.

Randomization

Participants were randomized 1:2:2 to receive intravitreal ranibizumab, 0.5 mg, every 4 weeks; faricimab, 6.0 mg, every 12 weeks after initiation (4 total injections every 4 weeks from baseline to week 12); or faricimab, 6.0 mg, every 16 weeks after initiation (4 total injections every 4 weeks from baseline

to week 12). Randomization was performed through an interactive voice and web response system (IxRS) and stratified for baseline BCVA (ETDRS letter score ≥55 vs ≤54).

Study Treatments and Assessments

Study treatment was administered up to week 48, with the final visit at week 52. The primary end point was at week 40. At week 24, disease activity was assessed using 6 per-protocol-defined criteria, based on changes in central subfield thickness (CST) and BCVA and any other disease activity per investigator opinion (eFigure 2 and eTable 2 in Supplement 2). Participants randomized to faricimab every 16 weeks who did not have disease activity at week 24 continued treatment every 16 weeks through study end, while participants with active disease at week 24 received treatment every 12 weeks through study end. Participants in the faricimab arm who received dosing every 16 weeks included both participants who, after the initial 4 monthly doses, continued dosing every 16 weeks through study end and those who received dosing every 12 weeks from week 24 owing to active disease detected at that time. Participants were not allowed to receive additional faricimab injections during the dosing periods for every 12 weeks or every 16 weeks. Although no rescue treatments were allowed in participants on study treatment protocol, as a safety precaution, participants could drop out of study treatment and initiate standard of care (anti-VEGF).

STAIRWAY was a patient- and outcome assessor (BCVA and central reading center)–masked trial that allowed for a single investigator per site while fulfilling masking requirements. Study participants and BCVA examiners were masked to treatment assignment. The investigator administering the patient's treatment and/or designated personnel responsible for study drug preparation was unmasked to treatment assignment. Central reading center personnel, study vendors, and the sponsor and its agents were masked to study eye drug assignment.

Outcomes

The primary efficacy outcome measure was mean change from baseline BCVA at week 40. Key secondary visual acuity outcome measures were mean change from baseline BCVA evaluated monthly over time and proportion of participants gaining or not losing at least 15, at least 10, at least 5, or at least 0 ETDRS letters from baseline over time. Key secondary anatomic outcome measures were mean change from baseline in CST over time using SD-OCT and mean change from baseline in total lesion area and area of total lesion leakage at weeks 40 and 52 using FA.

Exploratory outcome measures included proportion of participants with disease activity at week 24. Safety outcome measures included incidence and severity of ocular and nonocular adverse events (AEs).

Statistical Analysis

Primary, secondary, and exploratory efficacy analyses were performed for all randomized participants, except for 5 participants excluded from all analyses owing to GCP noncompliance at a single site. The safety analysis population included all randomized participants (excluding 5 participants from the GCP noncompliance site) who received at least 1 dose of study treatment, whether prematurely withdrawn from the study or not.

Study sample size was determined assuming a common SD for BCVA change from baseline of 13.5 ETDRS letters, where distance from the difference of the means between faricimab and ranibizumab to the 2-sided 80% CI bounds was estimated to be 5.5 letters.

The primary efficacy analysis of BCVA change from baseline at week 40 was performed using a mixed model for repeated measurements, including the categorical covariates of treatment group, visit, and visit-by-treatment group interaction and the continuous covariate of baseline BCVA. An unstructured covariance was used to account for within-patient correlation. Formal statistical comparisons were not performed across treatment arms for any efficacy end point. There was no formal type I error correction for multiple testing.

Secondary efficacy analysis of BCVA change from baseline over time was performed using a mixed model for repeated measurements as described earlier. Categorical outcomes measured repeatedly were based on observed data. Exploratory efficacy analysis of proportion of patients with disease activity at week 24 was reported with the corresponding 80% CIs by study arm. Data acquisition and data processing of the controls and samples were performed by Gen5 Secure Software, version 1.08 or higher. Analysis began January 2017 and ended March 2018.

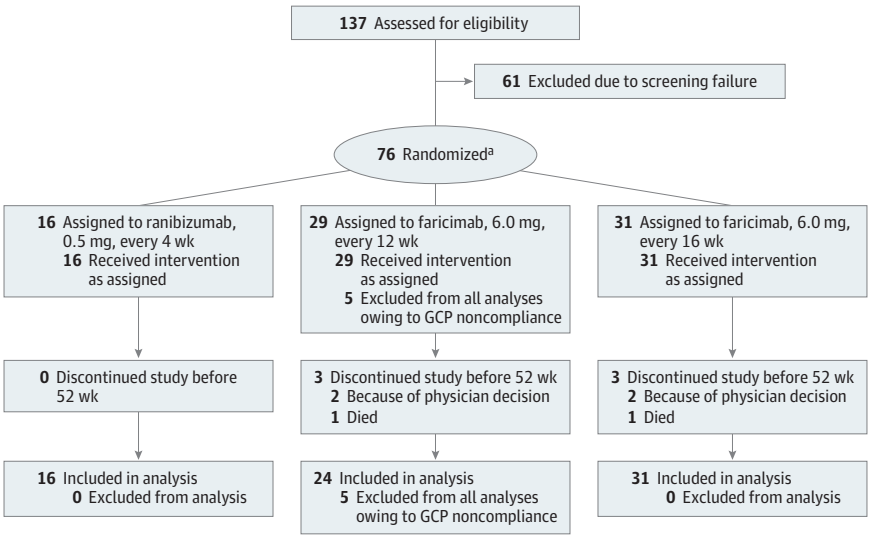
Results

STAIRWAY Enrollment and Patient Disposition

STAIRWAY enrolled 76 anti-VEGF treatment-naive patients with nAMD (**Figure 1** and eFigure 1 in Supplement 2). Enrolled participants received ranibizumab, 0.5 mg, every 4 weeks (16 [20.2%]); faricimab, 6.0 mg, every 12 weeks (29 [36.7%]); and faricimab, 6.0 mg, every 16 weeks (31 [39.2%]). Good Clinical Practice violations of data falsification 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 5 participants from this site were excluded from efficacy and safety analyses (including the safety-evaluable population) and did not demonstrate additional BCVA benefit or new safety signals compared with ranibizumab, 0.5 mg, every 4 weeks. Of 71 participants, 64 (90.1%) attended the primary end point week-40 visit, and 65 (91.5%) completed the study through week 52. Patient discontinuation was relatively balanced across the faricimab arms (Figure 1). Overall, the reasons from discontinuation were: (1) noncompliance with study visits (1 [1.4%]), (2) death (3 [4.2%]), (3) principal investigator (A.M.K.) wanted to treat with standard of care instead (1 [1.4%]), and (4) disease activity detected (1 [1.4%]).

At least 1 major protocol deviation was reported for 7 participants (9.9%). All protocol deviations were considered to be procedural and had no meaningful effect on the safety and efficacy findings.

Figure 1. CONSORT Flow Diagram of the STAIRWAY Study



Patients were randomized 1:2:2 into the ranibizumab, 0.5 mg, every 4 weeks; faricimab, 6.0 mg, every 12 weeks; and faricimab, 6.0 mg, every 16 weeks treatment arms. Only 1 eye was chosen as the study eye.

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

Table 1. Baseline Patient Demographics and Ocular Characteristics

Characteristic	Ranibizumab, 0.5 mg, every 4 wk (n = 16)	Faricimab, 6.0 mg, every 12 wk (n = 24)	Faricimab, 6.0 mg, every 16 wk (n = 31)	All participants (N = 71)
Age, mean (SD), y	77.3 (10.29)	80.3 (7.23)	77.7 (8.38)	78.5 (8.47)
Female, No. (%)	10 (62.5)	13 (54.2)	18 (58.1)	41 (57.7)
Race, No. (%)				
Asian	0	0	1 (3.2)	1 (1.4)
Black or African American	0	1 (4.2)	0	1 (1.4)
White	16 (100.0)	23 (95.8)	30 (96.8)	69 (97.2)
BCVA, mean (SD), ETDRS letters	55.3 (12.1)	57.8 (10.5)	60.4 (10.8)	58.4 (11.0)
CST, mean (SD), µm	443.1 (125.0)	417.9 (84.3)	382.2 (80.9)	408.0 (95.4)
CNV lesion type, No. (%)				
Classic and occult	6 (37.5)	9 (37.5)	9 (29.0)	24 (33.8)
Classic	2 (12.5)	0	2 (6.5)	4 (5.6)
Occult	8 (50.0)	15 (62.5)	20 (64.5)	43 (60.6)
Total lesion area, mean (SD), mm^2	7.3 (2.9)	7.1 (3.9)	5.9 (3.8)	6.6 (3.6)
Area of total lesion leakage, mean (SD), mm^2	7.6 (2.9)	7.1 (3.8)	6.1 (3.4)	6.7 (3.5)

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

Baseline Characteristics

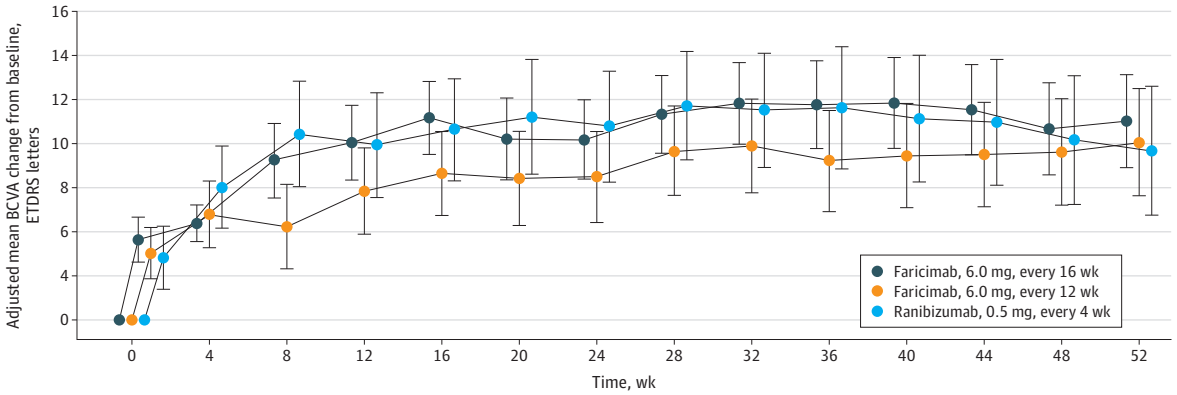
Baseline patient demographics and ocular characteristics in STAIRWAY were generally balanced across treatment arms (**Table 1**). The mean (SD) age for all participants was 78.5 (8.5) years (range, 56-94 years), and 41 participants (58%) were female. Small differences in baseline BCVA and CST across arms were observed owing to the relatively small sample size. Mean baseline BCVA ETDRS letter scores were 55.3 (approximate Snellen equivalent, 20/80), 57.8 (approximate Snellen equivalent, 20/63), and 60.4 (approximate Snellen equivalent, 20/63), respectively, in the ranibizumab arm with dosing every 4 weeks, faricimab arm with dosing every 12 weeks, and faricimab arm with dosing every 16 weeks; mean (SD) baseline CST as measured by SD-OCT was 443.1 (125.0) µm, 417.9 (84.3) µm, and 382.2 (80.9) µm, in the ranibizumab arm with dosing every 4 weeks, faricimab arm with dosing every 12 weeks, and faricimab arm with dosing every 16 weeks, respectively. The mean (SD) total lesion area as measured by FA was 7.3 (2.9) mm^2, 7.1 (3.9) mm^2, and 5.9 (3.8) mm^2, and the mean (SD) area of total lesion leakage was 7.6 (2.9) mm^2, 7.1 (3.8) mm^2, and 6.1 (3.4) mm^2, in the ranibizumab arm with dosing every 4 weeks, faricimab arm with dosing every 12 weeks, and faricimab arm with dosing every 16 weeks, respectively.

Efficacy Outcomes

Disease Activity Assessment

Disease activity in STAIRWAY was assessed using the per-protocol defined criteria shown in eFigure 2 and eTable 2 in Supplement 2. At week 24, 12 weeks after the last loading dose, 65% (36 of 55) of all faricimab-treated participants had no

Figure 2. Key Vision Outcome: BCVA Change From Baseline Over Time



Sample size, No.														
Ranibizumab, 0.5 mg, every 4 wk	16	16	15	16	16	16	16	16	16	16	15	16	16	16
Faricimab, 6.0 mg, every 12 wk	24	24	24	23	23	23	23	23	23	22	21	20	21	21
Faricimab, 6.0 mg, every 16 wk	31	31	30	30	30	30	30	30	30	29	28	29	28	28

Least squares means from linear model analysis of study eye best-corrected visual acuity (BCVA) change from baseline. Model includes categorical covariates of treatment group, visit, visit-by-treatment group interaction, and the continuous covariate of baseline BCVA. For those taking ranibizumab, 0.5 mg, every 4 weeks, there was a mean change of 9.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters after a mean of 12.9 injections to week 52. For those taking faricimab, 6.0 mg, every 12 weeks, there was a mean change of 10.1 ETDRS letters after a mean of 6.7 injections to week 52. For those taking faricimab, 6.0 mg, every 16 weeks, there was a mean change of 11.4 ETDRS letters after a mean of 6.2 injections to week 52. Error bars represent 80% CIs.

disease activity. In the faricimab arm with dosing every 16 weeks, 61% (19 of 31) of participants had no disease activity at week 24 and were qualified to continue receiving a dosing regimen every 16 weeks through study end (with the exception of 1 patient who discontinued prior to week 24). In the faricimab arm with dosing every 12 weeks, 71% (17 of 24) of participants showed no signs of disease activity at week 24. Ninety-four percent (15 of 16) of participants in the ranibizumab arm with dosing every 4 weeks had no disease activity at week 24, 4 weeks after the last ranibizumab dose.

Participants randomized to the faricimab arms with dosing every 16 weeks and with dosing every 12 weeks achieved visual acuity gains comparable with participants randomized to the ranibizumab arm with dosing every 4 weeks but with fewer injections. Including the initial 4 monthly initiation injections for faricimab participants, participants received a mean (SD) of 12.9 (0.25), 6.7 (0.91), and 6.2 (0.93) total injections in the ranibizumab arm of dosing every 4 weeks, faricimab arm of dosing every 12 weeks, and faricimab arm of dosing every 16 weeks, respectively, over 52 weeks. No additional injections were allowed other than the assigned dosing intervals in the faricimab arm of dosing every 16 weeks or arm of dosing every 12 weeks.

Visual Acuity Outcomes

At the primary end point of week 40, faricimab treatment with dosing every 16 weeks and dosing every 12 weeks resulted in vision gains comparable with ranibizumab fixed dosing every 4 weeks (**Figure 2** and eTable 3 in Supplement 2).

The proportion of participants gaining at least 15 ETDRS letters from baseline and proportion not losing at least 15 ETDRS letters from baseline at weeks 40 and 52 are provided in eTable 3 in Supplement 2. The proportion of participants gaining or not losing at least 10, at least 5, and at least 0 ETDRS letters from baseline at weeks 40 and 52 are provided in eTable 4 in Supplement 2.

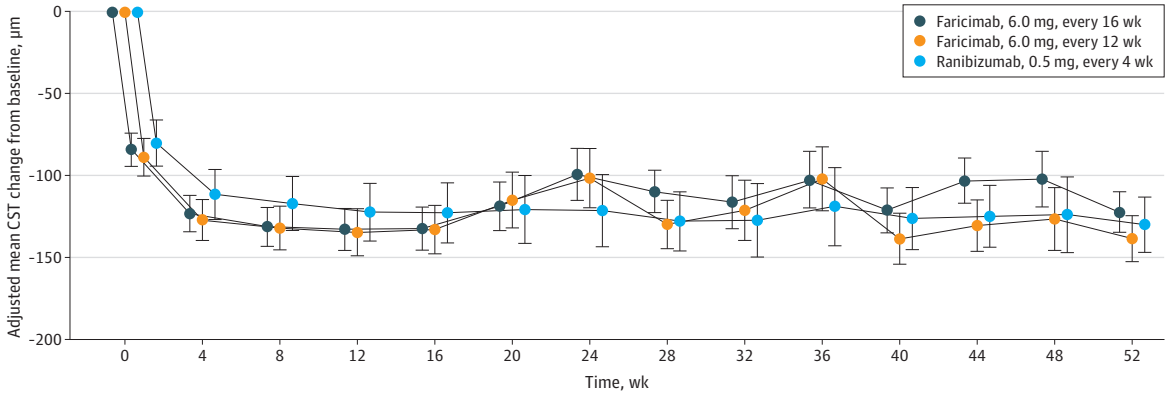
Anatomic Outcomes

Anatomic outcomes as assessed by SD-OCT and FA at weeks 40 and 52 support the visual acuity outcomes in STAIRWAY (eTable 3 in Supplement 2). Treatment with faricimab dosing every 16 weeks and faricimab dosing every 12 weeks resulted in CST reductions and changes in total lesion area comparable with ranibizumab treatment (**Figure 3** and eTable 3 and eFigure 3 in Supplement 2).

Safety Outcomes

The safety analysis population included all randomized participants (excluding 5 participants from a single site owing to GCP noncompliance) who received at least 1 dose of study treatment, withdrawn from the study or not. Key ocular and nonocular safety events are shown in **Table 2.** Of 71 participants, 54 (76.1%) experienced at least 1 AE (ranibizumab every 4 weeks, 81.3% [13 of 16]; faricimab every 12 weeks, 75.0% [18 of 24]; faricimab dosing every 16 weeks, 74.2% [23 of 31]). Overall, 39.4% (28 of 71) of participants experienced an ocular AE in the study eye (Table 2). There were no serious ocular AEs in the study or fellow eyes. Sixty-one percent (43 of 71) of participants experienced at least 1 nonocular AE (Table 2), but none were considered related to study treatment. No AEs were reported that led to discontinuation of treatment. Three participants experienced AEs with a fatal outcome, due to either ischemic stroke (faricimab every 12 weeks), sepsis (faricimab dosing every 16 weeks), or metastatic neoplasm (faricimab dosing every 16 weeks); none were considered related to study treatment per the study investigator's assessment. Full listings of ocular and nonocular safety events are

Figure 3. Key Anatomic Outcomes



Sample size, No.														
Ranibizumab, 0.5 mg, every 4 wk	16	16	15	16	16	16	16	16	16	16	15	16	16	16
Faricimab, 6.0 mg, every 12 wk	24	24	24	22	23	23	23	23	23	22	21	20	21	21
Faricimab, 6.0 mg, every 16 wk	31	31	30	30	30	30	30	30	30	29	27	29	28	28

Central subfield thickness (CST) reduction from baseline over time. Least squares means from linear model analysis of study eye CST change from baseline. Model includes categorical covariates of treatment group, visit, visit-by-treatment group interaction, and the continuous covariate of baseline CST. For those taking ranibizumab, 0.5 mg, every 4 weeks, there was a mean change of −129.9 µm. For those taking faricimab, 6.0 mg, every 12 weeks, there was a mean change of −138.5 µm. For those taking faricimab, 6.0 mg, every 16 weeks, there was a mean change of −122.5 µm. Error bars represent 80% CIs.

Table 2. Key Ocular and Nonocular AEs

Selected AEs[a]	No. (%)		
	Ranibizumab, 0.5 mg, every 4 wk (n = 16)	Faricimab, 6.0 mg, every 12 wk (n = 24)	Faricimab, 6.0 mg, every 16 wk (n = 31)
Ocular AE (study eye)	8 (50.0)	9 (37.5)	11 (35.5)
Serious ocular AE (study eye)	0	0	0
Nonocular AE	9 (56.3)	14 (58.3)	20 (64.5)
Serious nonocular AE	0	4 (16.7)[b]	3 (9.7)[c]
Intraocular inflammation[d]	0	1 (4.2)	1 (3.2)
Endophthalmitis	0	0	0
Retinal detachment	0	0	0
Vitreous hemorrhage	0	0	1 (3.2)
Hypertension	1 (6.3)	0	1 (3.2)
APTC events			
Nonfatal myocardial infarction	0	0	0
Nonfatal stroke	0	1 (4.2)	0
Vascular or cardiac death or death or unknown cause	0	1 (4.2)[e]	0
Combined APTC events	0	2 (8.3)	0
Any other death	0	0	2 (6.5)[f]
IOP increased	1 (6.3)	0	0

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

[a] Study eye or nonocular; total participants with ≥1 AE. Multiple occurrences of the same event in 1 individual counted only once.

[b] Seven events in 4 patients: acute left ventricular failure, coronary artery disease, fall, headache, ischemic stroke, mental status changes, and vertigo.

[c] Three events in 3 patients: atrial fibrillation, metastatic neoplasm, and sepsis.

[d] Defined as all AEs that are potentially indicative of intraocular inflammation as reported by the investigator, including flares and cells in the anterior chamber of any severity; 1 case of mild iritis and 1 case of mild anterior chamber flare.

[e] Ischemic stroke.

[f] Sepsis, metastatic neoplasm.

provided in eTables 5, 6, and 7 in Supplement 2. Overall, faricimab was well tolerated, and there were no new or unexpected safety events observed in STAIRWAY.

Discussion

In the STAIRWAY phase 2 study of faricimab for nAMD, initial vision gains were maintained with faricimab dosing every 16 weeks and dosing every 12 weeks over 52 weeks. No clinically important differences between the faricimab and ranibizumab treatment arms were identified. The results with faricimab support further exploration in the phase 3 trials. There were no new or unexpected safety events in STAIRWAY, comparable with the overall safety profile across the faricimab phase 1 and phase 2 studies (AVENUE, STAIRWAY, and BOULEVARD) that enrolled nearly 600 patients.[16,20,23] Simultaneous neutralization of Ang-2 and VEGF-A with faricimab may allow for fewer injections, addressing the high unmet need for more sustained treatments in the real world (**Video**).

The sustained efficacy potential of faricimab with dosing every 16 weeks, as shown in STAIRWAY, has not been demonstrated in any of the previous nAMD studies with anti-VEGF monotherapy injections. Extending to dosing every 16 weeks as shown in STAIRWAY has never been tried in previous nAMD trials, to our knowledge. This study did not intend to directly compare performance of faricimab with ranibizumab dosage using treat-and-extend regimen because this is not a dosing regimen accepted by the US Food and Drug Administration for use of ranibizumab in nAMD. Although there have been multiple clinical trials, for example, PIER, EXCITE, and VIEW (VIEW 1 and VIEW 2), that have studied less frequent than monthly dosing with ranibizumab, BCVA outcomes have not been shown to be equivalent to those reported with monthly dosing. Therefore, to maximize visual acuity gains with ranibizumab, the US Food and Drug Administration recommends monthly dosing. The heterogeneity of anti-VEGF response in the nAMD population poses a challenge for implementing such low-frequency regimens in studies, which has previously been associated with mean loss of vision from baseline. For example, the clinical trials PIER, EXCITE, and VIEW (VIEW 1 and VIEW 2) investigated dosing every 12 weeks with anti-VEGF agents, without the possibility of rescue injections, and showed a decline in BCVA gains, on average, across their nAMD study populations.[24-26] Even with careful monitoring, only approximately half of patients with nAMD can be extended to dosing every 12 weeks with anti-VEGF monotherapy injections, including with the next-generation anti-VEGF agent brolucizumab.[27]

The prespecified dosing regimen of every 16 weeks, where participants had the opportunity to receive dosing every 12 weeks based on their early response to faricimab treatment at week 24, compensated for the lack of predictive injection frequency biomarkers in the heterogeneous nAMD population. Week 24 was 12 weeks since the last injection for all faricimab participants and only 4 weeks since the last injection for ranibizumab participants. While overall BCVA and CST values were comparable across the faricimab dosing arm of every 12 weeks and dosing arm of every 16 weeks and the ranibizumab dosing arm of every 4 weeks at week 24, higher disease activity rates were detected in the faricimab dosing every 12 weeks and dosing every 16 weeks arms compared with the ranibizumab dosing every 4 weeks arm. This discrepancy in disease activity rates at week 24 did not result in overall major BCVA or CST change, on average, as shown by no detectable difference among treatment arms on BCVA and CST. In addition to CST change, the disease activity criteria also included BCVA loss due to nAMD activity, presence of hemorrhage, and investigator opinion. Therefore, in a proportion of cases, qualitative changes on OCT may have contributed to investigator determination of active disease. These results indicate a lack of correlation between OCT changes and BCVA outcomes in the nAMD population and also support the ongoing debate regarding the importance of subretinal fluid, OCT fluctuation, and drying on vision maintenance.[28,29]

Limitations

A limitation of STAIRWAY was the relatively small sample size. As a phase 2 study with 71 participants analyzed, the typical post hoc analyses of patient subgroups would be challenging to interpret. Formal statistical comparisons were not performed across the treatment arms. Also, the vascular stability effect of Ang-2 neutralization may require a longer study, and OCT and FA alone may not be sufficient to assess the full effect of Ang-2 neutralization. Additionally, more advanced imaging methodologies may be able to provide improved understanding of the faricimab mechanism of action.

Conclusions

In conclusion, the faricimab dosing regimen every 16 weeks resulted in maintenance of initial vision and anatomic improvements throughout 52 weeks that were comparable with outcomes achieved with monthly ranibizumab injections, extending results of the larger AVENUE phase 2 trial.[16] The phase 3, identically designed, randomized, controlled, statistically powered clinical trials TENAYA (NCT03823287) and LUCERNE (NCT03823300) are currently underway and will validate whether STAIRWAY durability outcomes are reproducible across a larger population. By demonstrating comparable outcomes with anti-VEGF monotherapy with fewer injections in STAIRWAY, faricimab demonstrated its potential to provide sustained efficacy through extended durability and reduce treatment burden.

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Invited Commentary

Faricimab Combination Therapy for Sustained Efficacy in Neovascular Age-Related Macular Degeneration

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The advent of anti-vascular endothelial growth factor (anti-VEGF) therapy has represented a paradigm shift in the treatment of neovascular age-related macular degeneration (nAMD). However, anti-VEGF injections require frequent office visits for administration to maintain visual acuity gains, placing a considerable treatment burden on patients, caregivers, and the health care system. Achieving sustained efficacy with fewer injections has been a major focus of research into new therapeutic options for nAMD.

Related article page 964

In this issue of *JAMA Ophthalmology*, Khanani et al[1] report the results of the STAIRWAY trial, a phase 2 clinical trial designed to evaluate faricimab in patients with nAMD. Faricimab differs from the currently approved agents for nAMD because of its action against both VEGF-A and angiopoietin (Ang)-2.[2] The angiopoietins Ang-1 and Ang-2 play key roles in vascular homeostasis and angiogenesis.[3,4] Both Ang-1 and Ang-2 bind to the tyrosine kinase with immunoglobulinlike domains 2 (Tie2) receptor on vascular endothelial cells. Ang-1 signaling protects from pathological angiogenesis and maintains a quiescent, mature vessel phenotype.[3] Ang-2 competitively inhibits Ang-1 signaling through Tie2, thus promoting vascular leakage and abnormal vessel structure.[4] Faricimab was developed as RG7716, a human monoclonal antibody made up of 2 different heavy chains and 2 different light chains, with 1 antigen-binding domain that binds VEGF-A and 1 that binds Ang-2.[2] Preclinical studies demonstrated that faricimab neutralizes both human VEGF-A and Ang-2 simultaneously without binding to Ang-1.[2] In a nonhuman primate, laser-induced choroidal neovascularization model,[2] neutralization of both VEGF-A and Ang-2 reduced vessel leakiness and choroidal neovascularization lesion number more effectively than either agent alone.

The BOULEVARD phase 2 clinical trial[5] evaluated faricimab for diabetic macular edema. Patients were randomized to receive 6.0 mg of faricimab, 1.5 mg of faricimab, or 0.3 mg of ranibizumab every 4 weeks, and the primary end point outcomes were measured at 24 weeks. Patients who were naive to treatment who received 6.0 mg of faricimab achieved a statistically significant gain of visual acuity compared with those treated with 0.3 mg of ranibizumab. The BOULEVARD trial also assessed the length of time for each patient to meet predefined criteria for disease reactivation during a subsequent 12-week observation period. Patients who received 6.0 mg of faricimab were more likely to have a longer time to reactivation compared with those who received 0.3 mg of ranibizumab. These findings suggested that faricimab may have sustained efficacy compared with ranibizumab for patients with diabetic macular edema.

The STAIRWAY trial[1] was designed to test the sustained efficacy of faricimab in nAMD. Patients who were naive to treatment were randomized to receive 6.0 mg of faricimab every 12 weeks after 4 initial doses every 4 weeks, 6.0 mg of faricimab every 16 weeks after 4 initial doses every 4 weeks (flex), or 0.5 mg of ranibizumab every 4 weeks. Patients in the flex arm who met predefined criteria for disease activity 12 weeks after the last loading dose received injections every 12 weeks from that point on. At the 24-week point, 39% of patients in the flex arm, 29% of patients receiving faricimab every 12 weeks, and 6% of patients in the arm receiving ranibizumab every 4 weeks showed signs of disease activity.

However, despite differences in the presence of anatomic signs of disease activity, visual acuity gains at the primary end point of 40 weeks and the last study visit at 52 weeks were similar between the arms receiving faricimab every 12 weeks, faricimab every 16 weeks, and ranibizumab every 4 weeks.[1] The mean total numbers of injections through week 52 were 6.7, 6.2, and 12.9, respectively. Thus, extended dosing with faricimab resulted in visual improvements comparable with monthly ranibizumab in individuals with nAMD who were treatment naive, which supports its potential to provide sustained efficacy.[1]

One consideration in thinking about these results[1] is whether administration of a higher anti-VEGF dose could partly explain the sustained outcome in the faricimab study arms.