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Authors

Khanani, Arshad M

Kotecha, Aachal

Chang, Andrew

et al.

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TENAYA and LUCERNE

Two-Year Results from the Phase 3 Neovascular Age-Related Macular Degeneration Trials of Faricimab with Treat-and-Extend Dosing in Year 2

Arshad M. Khanani, MD, MA,[1] Aachal Kotecha, PhD,[2] Andrew Chang, MBBS, PhD,[3] Shih-Jen Chen, MD,[4] Youxin Chen, MD,[5] Robyn Guymer, MBBS, PhD,[6] Jeffrey S. Heier, MD,[7] Frank G. Holz, MD,[8] Tomohiro Iida, MD,[9] Jane A. Ives, MSc,[2] Jennifer I. Lim, MD,[10] Hugh Lin, MD, MBA,[11] Stephan Michels, MD, MBA,[12,13] Carlos Quezada Ruiz, MD, FASRS,[11] Ursula Schmidt-Erfurth, MD,[14] David Silverman, MSc, MBChB,[2] Rishi Singh, MD, FASRS,[15] Balakumar Swaminathan, MSc,[16] Jeffrey R. Willis, MD, PhD,[11] Ramin Tadayoni, MD, PhD,[17] for the TENAYA and LUCERNE Investigators

Purpose: To evaluate 2-year efficacy, durability, and safety of the bispecific antibody faricimab, which inhibits both angiopoietin-2 and VEGF-A.

Design: TENAYA (ClinicalTrials.gov identifier, NCT03823287) and LUCERNE (ClinicalTrials.gov identifier, NCT03823300) were identically designed, randomized, double-masked, active comparator-controlled phase 3 noninferiority trials.

Participants: Treatment-naive patients with neovascular age-related macular degeneration (nAMD) 50 years of age or older.

Methods: Patients were randomized (1:1) to intravitreal faricimab 6.0 mg up to every 16 weeks (Q16W) or aflibercept 2.0 mg every 8 weeks (Q8W). Faricimab fixed dosing based on protocol-defined disease activity at weeks 20 and 24 up to week 60, followed up to week 108 by a treat-and-extend personalized treatment interval regimen.

Main Outcome Measures: Efficacy analyses included change in best-corrected visual acuity (BCVA) from baseline at 2 years (averaged over weeks 104, 108, and 112) and proportion of patients receiving Q16W, every 12 weeks (Q12W), and Q8W dosing at week 112 in the intention-to-treat population. Safety analyses included ocular adverse events (AEs) in the study eye through study end at week 112.

Results: Of 1326 patients treated across TENAYA/LUCERNE, 1113 (83.9%) completed treatment (n = 555 faricimab; n = 558 aflibercept). The BCVA change from baseline at 2 years was comparable between faricimab and aflibercept groups in TENAYA (adjusted mean change, +3.7 letters [95% confidence interval (CI), +2.1 to +5.4] and +3.3 letters [95% CI, +1.7 to +4.9], respectively; mean difference, +0.4 letters [95% CI, −1.9 to +2.8]) and LUCERNE (adjusted mean change, +5.0 letters [95% CI, +3.4 to +6.6] and +5.2 letters [95% CI, +3.6 to +6.8], respectively; mean difference, −0.2 letters [95% CI, −2.4 to +2.1]). At week 112 in TENAYA and LUCERNE, 59.0% and 66.9%, respectively, achieved Q16W faricimab dosing, increasing from year 1, and 74.1% and 81.2%, achieved Q12W or longer dosing. Ocular AEs in the study eye were comparable between faricimab and aflibercept groups in TENAYA (55.0% and 56.5% of patients, respectively) and LUCERNE (52.9% and 47.5% of patients, respectively) through week 112.

Conclusions: Treat-and-extend faricimab treatment based on nAMD disease activity maintained vision gains through year 2, with most patients achieving extended dosing intervals.

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Age-related macular degeneration (AMD) is a leading cause of visual impairment and severe vision loss.[1,2] As a multifactorial disease, numerous processes and pathways contribute to the pathogenesis of AMD,[3] with VEGF-A shown to play a key role in neovascular AMD (nAMD).[4] Use of intravitreal anti-VEGF therapy as current standard of care for treatment of nAMD has improved vision outcomes for many patients, resulting in a reduction in severe

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vision loss as a result of this disease.[4] However, long-term treatment outcomes for nAMD in clinical practice often are not as successful as in prospective randomized clinical trials. One likely explanation for this is undertreatment resulting from the treatment burden of frequent monitoring and intravitreal injections when using anti-VEGF therapy,[4] particularly in an elderly population. More durable therapies with reduced injection frequencies are needed, and approaches have focused on pursuing novel nAMD targets other than just VEGF, such as the angiopoietin−Tie2 pathway. In addition, despite the benefits of anti-VEGF treatment, many patients continue to lose vision because of the onset of fibrosis and outer retinal atrophy, neither of which are addressed by anti-VEGF alone.[5] Targeted inhibition of novel pathways has the potential to improve treatment outcomes and durability for patients with nAMD.[5,6]

In healthy retinal vessels, the angiopoietin−Tie2 signaling pathway helps to regulate angiogenesis and maintain vascular stability. In pathologic conditions such as nAMD, angiopoietin-2 levels are elevated, which inhibits angiopoietin-1 signaling and synergizes with upregulated VEGF-A to induce vascular instability via vascular leakage, inflammation, and neovascularization.[5,7] Therefore, a multitargeted approach with simultaneous inhibition of angiopoietin-2 and VEGF-A pathways may result in more durable efficacy through vascular stabilization, improving outcomes beyond VEGF inhibition alone.

Faricimab is the first and only bispecific antibody designed for intraocular use that independently binds and neutralizes angiopoietin-2 and VEGF-A.[8] TENAYA and LUCERNE were phase 3 trials of faricimab up to every 16 weeks (Q16W) compared with aflibercept every 8 weeks (Q8W) in patients with nAMD.[9] These randomized clinical trials each met their primary end point of noninferiority in mean change from baseline in best-corrected visual acuity (BCVA) at 1 year with faricimab compared with aflibercept.[9] The findings also showed meaningful reductions in central subfield thickness (CST) from baseline that were greater with faricimab than aflibercept during the matched-dosing period until week 12[10] and were comparable during the maintenance period. These visual and anatomic outcomes were achieved with most faricimab-treated patients on extended fixed-dosing regimens (approximately 80% receiving every 12 weeks [Q12W] or longer dosing and approximately 45% of faricimab-treated patients receiving Q16W dosing) at week 48. Faricimab was demonstrated to be well tolerated up to week 48 and showed a safety profile comparable with that of aflibercept.[9] The results of the primary analysis from the TENAYA and LUCERNE trials, as well as those from the phase 3 YOSEMITE and RHINE trials in patients with diabetic macular edema, demonstrated the durable efficacy and safety of faricimab up to 1 year[9,11] and subsequently informed the approval of faricimab for these indications in the United States[12] and in more than 70 countries in the Americas, Europe, and Asia-Pacific.

Notably, in the TENAYA and LUCERNE trials, a treat-and-extend (T&E) personalized treatment interval (PTI) regimen was introduced at the beginning of year 2 to allow patient dosing to be individualized based on disease activity after fixed treatment intervals during the first year.[9] Herein, we present the 2-year outcomes from the phase 3 TENAYA and LUCERNE trials to evaluate the long-term efficacy, durability, and safety of faricimab in patients with nAMD.

Methods

TENAYA and LUCERNE

TENAYA (ClinicalTrials.gov identifier, NCT03823287) and LUCERNE (ClinicalTrials.gov identifier, NCT03823300) were identically designed, randomized, double-masked, active comparator-controlled phase 3 trials conducted across 271 clinical sites worldwide.[9,13] The human ethics committees institutional review boards listed in the Appendix (available at www.aaojournal.org) approved the study. Both trials were carried out in accordance with the tenets of the Declaration of Helsinki and principles of Good Clinical Practice, and the study protocols were approved by appropriate regulatory authorities, applicable institutional review boards, and ethics committees. All patients provided written informed consent to participate.

Eligible patients were at least 50 years of age with treatment-naive choroidal neovascularization (CNV) secondary to nAMD; subfoveal CNV or juxtafoveal or extrafoveal CNV, with a subfoveal component related to CNV activity on OCT, CNV exudation, or both; CNV lesion size of 9 disc areas or less and CNV component area of 50% or more of the total lesion area on fundus fluorescein angiography; and BCVA of 78 to 24 ETDRS letters (approximate Snellen equivalent, 20/32−20/320). The full eligibility criteria for TENAYA and LUCERNE are available in the appendix of the 1-year primary publication.[9]

Patients were randomized 1:1 to faricimab 6.0 mg up to Q16W after 4 initial doses given every 4 weeks or aflibercept 2.0 mg Q8W after 3 initial doses given every 4 weeks. The primary publication reports additional details on randomization and masking.[9] After the initial 4 doses, patients in the faricimab arm were treated Q16W, Q12W, or Q8W through week 60. Dosing decisions in the first year were determined by a strict set of protocol-defined disease activity criteria at weeks 20 and 24 based on anatomic and BCVA measurements.[9,13] After week 60, faricimab-treated patients followed a T&E PTI regimen in a masked fashion up to week 108. During this T&E phase, dosing intervals were adjusted based on prespecified criteria of BCVA, spectral-domain OCT-determined CST measurements, presence of new macular hemorrhage, or a combination thereof (Table S1, available at www.aaojournal.org). In brief, dosing intervals could be extended by 4 weeks (up to Q16W) if the patient achieved stable anatomic features, vision, and no new macular hemorrhage. The interval was reduced by 4- or 8-week increments (as low as Q8W) if worsening vision or anatomic features were found, or new macular hemorrhage occurred (Table S1). If none of the extension or reduction criteria were met at study drug dosing visits, then the dosing interval was maintained. All patients were seen at study visits every 4 weeks and received active or sham treatment up to week 108 to preserve treatment masking, with an end-of-study nondosing visit at week 112[9,13]; patients were then given the opportunity to enter the AVONELLE-X extension study (ClinicalTrials.gov identifier, NCT04777201).

Key ocular assessments included BCVA, intraocular pressure, slit-lamp biomicroscopy, and dilated indirect ophthalmoscopy at

each study visit. Masked evaluators at central reading centers independently assessed ocular images obtained throughout the study (color fundus photography, fluorescein angiography, and spectral-domain OCT).

Outcome Measures

The primary efficacy end point of TENAYA and LUCERNE was change in BCVA from baseline at 1 year (averaged over weeks 40, 44, and 48).[9] Year 2 outcomes reported herein include change in BCVA from baseline at 2 years (averaged over weeks 104, 108, and 112) and over time; the proportion of patients gaining BCVA ($\geq$ 15 ETDRS letters, $\geq$ 10 ETDRS letters, $\geq$ 5 ETDRS letters, and $\geq$ 0 ETDRS letters) at 2 years; patients avoiding BCVA loss ($\geq$ 15 ETDRS letters, $\geq$ 10 ETDRS letters, and $\geq$ 5 ETDRS letters) at 2 years; patients with BCVA Snellen equivalent of 20/40 or better and 20/200 or worse at 2 years; the change in CST from baseline at 2 years (averaged over weeks 104, 108, and 112) and over time; the proportion of faricimab-treated patients receiving Q16W, Q12W, and Q8W dosing at week 112; and the incidence and severity of ocular adverse events (AEs) in the study eye and nonocular AEs through study end.

Statistical Analysis

The 2-year efficacy and safety analyses were performed as described in the primary analysis publication,[9] in which efficacy analyses were based on the intention-to-treat population, grouped by treatment arm assigned at randomization. Adjusted means for continuous end points were summarized using a mixed model for repeated measures that assumed an unstructured covariance structure; missing data were imputed implicitly assuming a missing at random mechanism. Weighted proportions of binary end points were estimated using the Cochran−Mantel−Haenszel method. COVID-19−related intercurrent events were handled using a hypothetical strategy in which all values were censored after the intercurrent event, and intercurrent events not related to COVID-19 were handled using a treatment policy strategy in which all observed values were used regardless of occurrence of the intercurrent event. Safety analyses included all randomized patients who received at least 1 dose of faricimab or aflibercept, grouped according to actual treatment received. Safety was assessed through descriptive summaries of ocular and nonocular AEs, deaths, and ocular assessments through study end. Adverse events were coded using the Medical Dictionary for Regulatory Activities thesaurus terms.

Results

Patient Disposition

A total of 989 patients with treatment-naive CNV secondary to nAMD were screened for eligibility in TENAYA between February 2019 and November 2019, and a total of 1012 patients were screened for eligibility in LUCERNE between March 2019 and November 2019 (Fig 1). Six hundred seventy-one patients met the eligibility criteria and were enrolled in TENAYA, with 334 patients randomized to the faricimab up to Q16W arm and 337 patients randomized to the aflibercept Q8W arm (Fig 1A). In LUCERNE, 658 patients met the eligibility criteria and were enrolled, with 331 patients randomized to the faricimab up to Q16W arm and 327 patients randomized to the aflibercept Q8W arm (Fig 1B). Most patients (84%) in the faricimab and aflibercept arms of TENAYA and LUCERNE completed study treatment through the end of the study. The proportion of patients who discontinued the study treatment and the main reasons for study discontinuation generally were balanced across treatment arms and trials (Fig 1).

Major protocol deviations were reported for 403 patients (60.1%; 190 patients [56.9%] in the faricimab group and 213 patients [63.2%] in the aflibercept group) in TENAYA and 350 patients (53.2%; 169 patients [51.1%] in the faricimab group and 181 patients [55.4%] in the aflibercept group) in LUCERNE through week 112 (Table S2, available at www.aaojournal.org). The number of patients, proportion of patients, and type of major protocol deviations through the study end were comparable between treatment arms and trials.

Major protocol deviations related to COVID-19 in the intention-to-treat population were reported in 185 patients (27.6%) in TENAYA and 167 patients (25.4%) in LUCERNE (Table S2). Through week 112, most of these deviations were the result of patients missing 1 or more study visits during the initial dosing phase or missing visits at the disease activity assessments preceding the primary end point, preceding the final study visit time points (137 patients [20.4%] and 118 patients [17.9%] in TENAYA and LUCERNE, respectively), or both. Among these, 28 patients (8.4%) in the faricimab arm and 32 patients (9.5%) in the aflibercept arm in TENAYA and 29 patients (8.8%) in the faricimab arm and 26 patients (8.0%) in the aflibercept arm in LUCERNE missed 1 or more doses of study treatment because of COVID-19 at any of these visits. Baseline patient characteristics in TENAYA and LUCERNE generally were well balanced across treatment arms and trials, as shown in the primary publication.[9]

Functional Outcomes

The clinically meaningful vision gains from baseline achieved during year 1 were maintained during year 2, with comparable vision gains between treatment arms (Fig 2) after implementation of the T&E PTI algorithm in year 2. At year 2 (averaged over weeks 104, 108, and 112), the adjusted mean change from baseline in BCVA was +3.7 ETDRS letters (95% confidence interval [CI], +2.1 to +5.4 ETDRS letters) in the faricimab up to Q16W arm and +3.3 ETDRS letters (95% CI, +1.7 to +4.9 ETDRS letters) in the aflibercept Q8W arm of TENAYA (mean difference vs. aflibercept Q8W: +0.4 ETDRS letters [95% CI, −1.9 to +2.8 ETDRS letters]). In LUCERNE, the corresponding 2-year BCVA gains from baseline were +5.0 ETDRS letters (95% CI, +3.4 to +6.6 ETDRS letters) versus +5.2 letters (95% CI, +3.6 to +6.8 ETDRS letters) in the faricimab and aflibercept arms, respectively (mean difference vs. aflibercept Q8W, −0.2 ETDRS letters [95% CI, −2.4 to +2.1 ETDRS letters]). In the pooled cohort, the adjusted mean change from baseline in BCVA at year 2 was +4.4 ETDRS letters (95% CI, 3.2−5.5 ETDRS letters) and +4.3 ETDRS letters (95% CI, 3.1−5.4 ETDRS letters) in the faricimab and aflibercept arms, respectively (Fig S3, available at www.aaojournal.org). Sensitivity and supplemental analyses to test the robustness of these results were consistent across different methods for handling missing data and intercurrent events (Table S3, available at www.aaojournal.org). Additional 2-year BCVA end points similarly were comparable across treatment arms and trials (Table S4, available at www.aaojournal.org).

Structural Outcomes

Reductions in CST observed from baseline to year 1 were maintained and stable through year 2 and were comparable between faricimab and aflibercept (Fig 4). At year 2 (averaged over weeks 104, 108, and 112), the adjusted mean change from baseline in

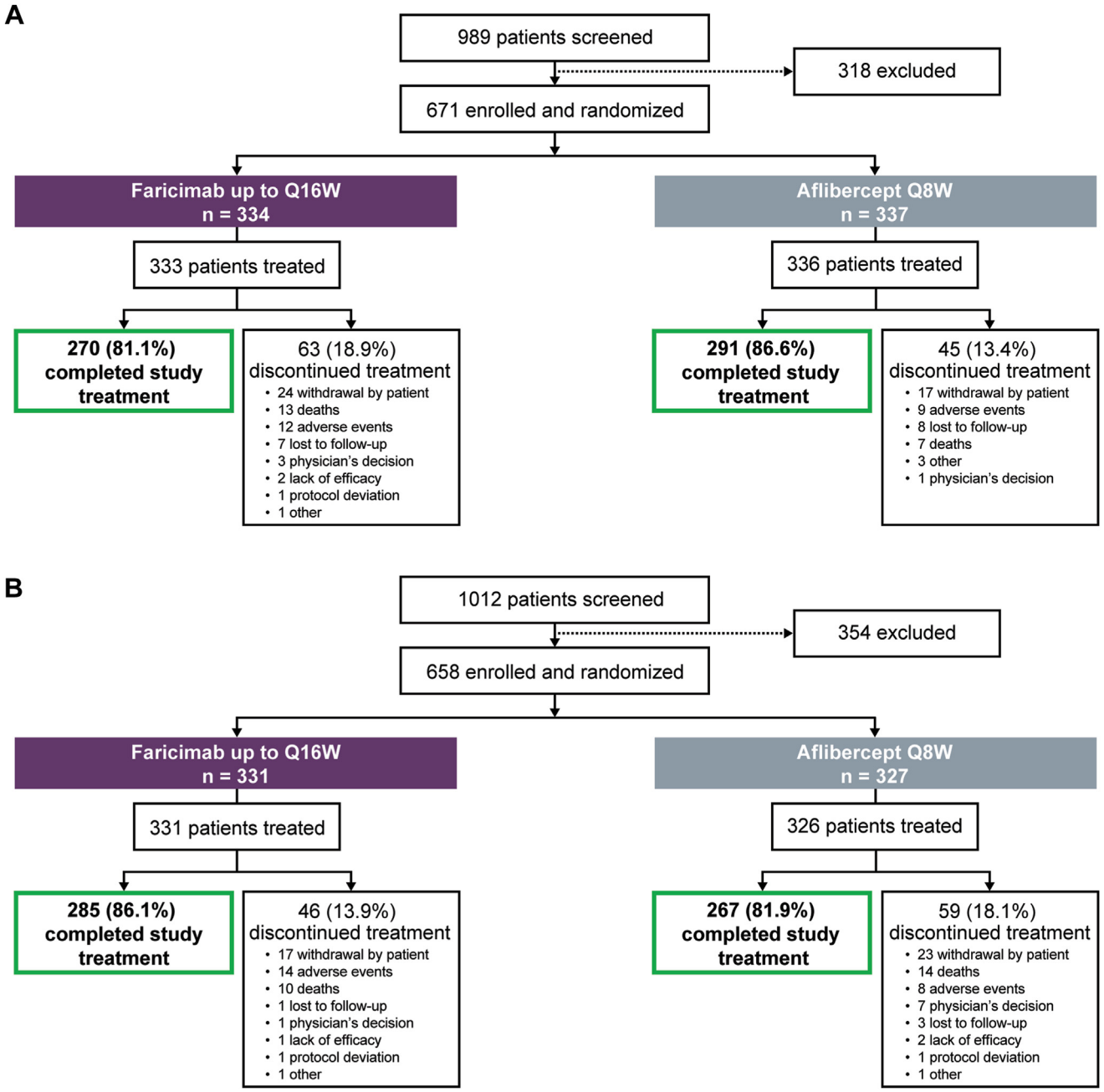

Figure 1. **A**, **B**, Consolidated Standards of Reporting Trials flow diagram for TENAYA (**A**) and LUCERNE (**B**). Q8W = every 8 weeks; Q16W = every 16 weeks.

CST was −146.5 μm (95% CI, −152.7 to −140.3 μm) in the faricimab up to Q16W arm and −146.2 μm (95% CI, −152.4 to −140.1 μm) in the aflibercept Q8W arm of TENAYA (mean difference vs. aflibercept Q8W, −0.3 μm [95% CI, −9.0 to +8.5 μm]). In LUCERNE, the corresponding 2-year CST reductions from baseline were −150.3 μm (95% CI, −156.1 to −144.6 μm) versus −141.6 μm (95% CI, −147.5 to −135.7 μm) in the faricimab and aflibercept arms, respectively (mean difference vs. aflibercept Q8W, −8.7 μm [95% CI, −17.0 to −0.5 μm]). In the pooled cohort, the adjusted mean change from baseline in CST at year 2 was −148.4 μm (95% CI, −152.7 to −144.2 μm) and −144.0 μm (95% CI, −148.3 to −139.8 μm) in the faricimab and aflibercept arms, respectively (Fig S5, available at www.aaojournal.org).

Durability Outcomes

The proportion of patients achieving Q16W dosing increased from approximately 45% in both trials at week 48[9] to 59.0% in TENAYA and 66.9% in LUCERNE (63.1% in the pooled TENAYA and LUCERNE cohort; Fig S6A, available at www.aaojournal.org) at week 112 (Fig 7A). The proportion of

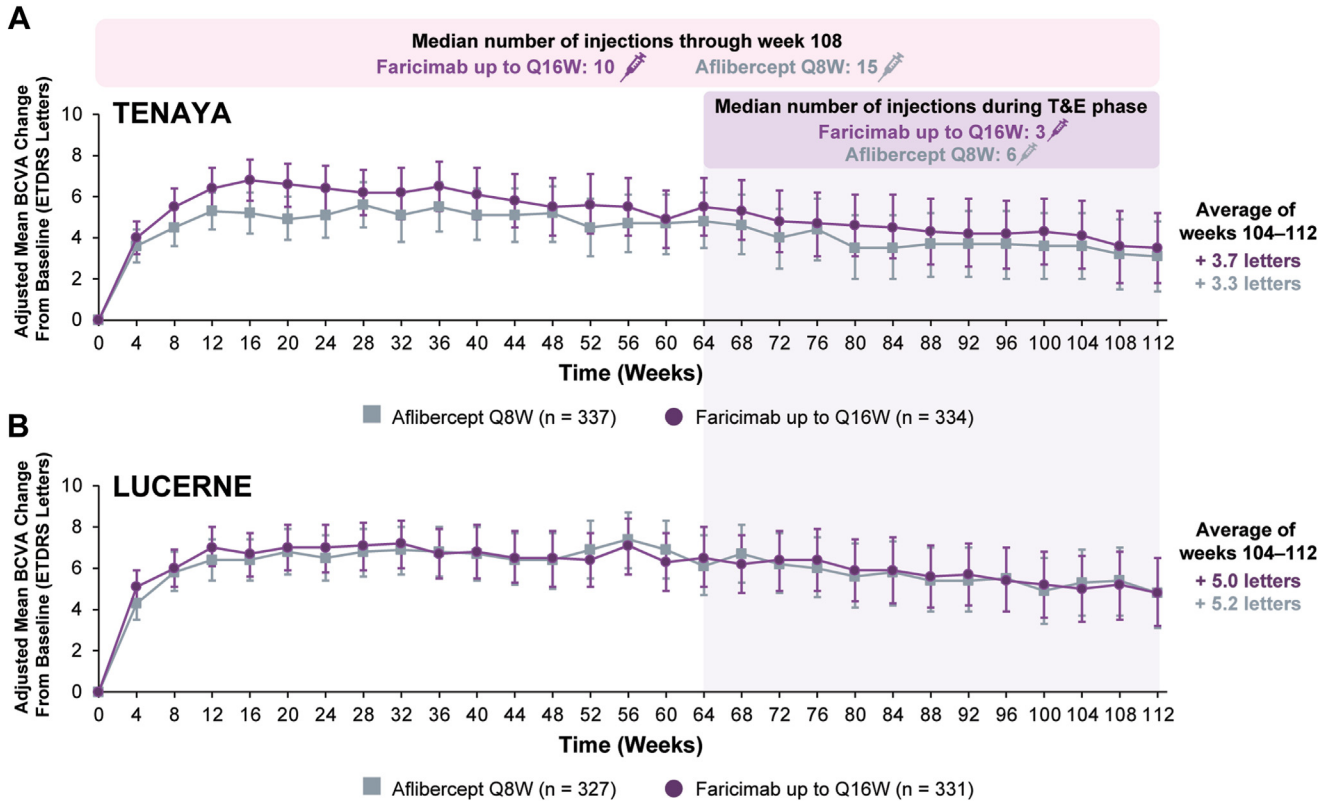

Figure 2. **A**, **B**, Line graphs showing the adjusted mean change in best-corrected visual acuity (BCVA) from baseline through week 112 and the number of active-treatment injections in each arm during the entire trial and treat-and-extend (T&E) personalized treatment interval phase of (**A**) TENAYA and (**B**) LUCERNE. Results are based on a mixed model for repeated measures (MMRM) analysis of the intention-to-treat population. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to coronavirus disease 2019 (COVID-19) and related to COVID-19, respectively. Missing data were imputed implicitly by the MMRM. Error bars represent the 95.03% confidence interval. Q8W = every 8 weeks; Q16W = every 16 weeks.

faricimab-treated patients receiving extended dosing (Q12W plus Q16W) in TENAYA and LUCERNE remained fairly similar between week 48 (79.7% and 77.8%, respectively)[9] and week 112 (74.1% and 81.2%, respectively; pooled, 77.8%; Fig 7A and Fig S6A). The comparable vision gains through year 2 in the faricimab arm were achieved with fewer injections than with aflibercept (Fig 2). In TENAYA and LUCERNE through year 2, the median number of faricimab injections was 10 (TENAYA: mean ± standard deviation [SD], 10.5 ± 2.86; LUCERNE: mean ± SD, 10.7 ± 2.68) compared with 15 aflibercept injections (TENAYA: mean ± SD, 13.8 ± 2.72; LUCERNE: mean ± SD, 13.5 ± 3.16). During the T&E PTI phase (after week 60), a median number of 3 faricimab injections (TENAYA: mean ± SD, 3.7 ± 1.21; LUCERNE: mean ± SD, 3.6 ± 1.19) were administered compared with 6 aflibercept injections (TENAYA: mean ± SD, 5.7 ± 0.84; LUCERNE: 5.7 ± 0.91) through week 112.

Figure 7B and Figure S6B show an overview of faricimab treatment patterns through week 112, with fixed dosing up to week 60 and T&E PTI dosing thereafter. Each row represents an individual patient over time, line color represents the dosing interval, and each box is a study visit. Most patients receiving extended dosing in year 1 were able to maintain or extend the dosing interval, or both, through year 2.

On average, 71% of patients who achieved the extended dosing interval of Q12W or longer during the fixed-dosing phase in year 1 maintained Q12W or longer dosing without a reduction to Q8W dosing during the T&E PTI dosing phase through year 2 (TENAYA, n = 143/215 patients [66.5%]; LUCERNE, n = 168/223 patients [75.3%]; Fig 7B and Fig S6B). Similarly, 69% of patients receiving Q16W dosing during the fixed-dosing phase in year 1 continued to receive that treatment interval without deviation during the T&E PTI dosing phase (TENAYA, n = 84/122 patients [68.9%]; LUCERNE, n = 93/135 patients [68.9%]).

On average, 59% of patients in the Q12W treatment interval group during the fixed-dosing phase were able to achieve Q16W dosing by week 112 (TENAYA, n = 46 patients [49.5%]; LUCERNE, n = 60 patients [68.2%]; Fig 7B and Fig S6B). On average, 56% of patients receiving Q8W dosing during the fixed-dosing phase were able to achieve an extended dosing interval (Q12W or Q16W) by week 112 (TENAYA: 29 patients [51.8%]; LUCERNE: 38 patients [59.4%]; Fig 7B and Fig S6B).

Safety Outcomes

Ocular and nonocular AEs through study end are summarized in Table 5, with further details given in Tables S6, S7, S8, and S9 (available at www.aaojournal.org). Consistent with the primary analysis up to 48 weeks,[9] faricimab continued to be well tolerated with an acceptable safety profile and remained comparable with aflibercept through study end at week 112. The proportion of patients experiencing ocular AEs in the study eye through week 112 was similar between treatment arms in TENAYA (faricimab up to Q16W, 183 patients [55.0%];

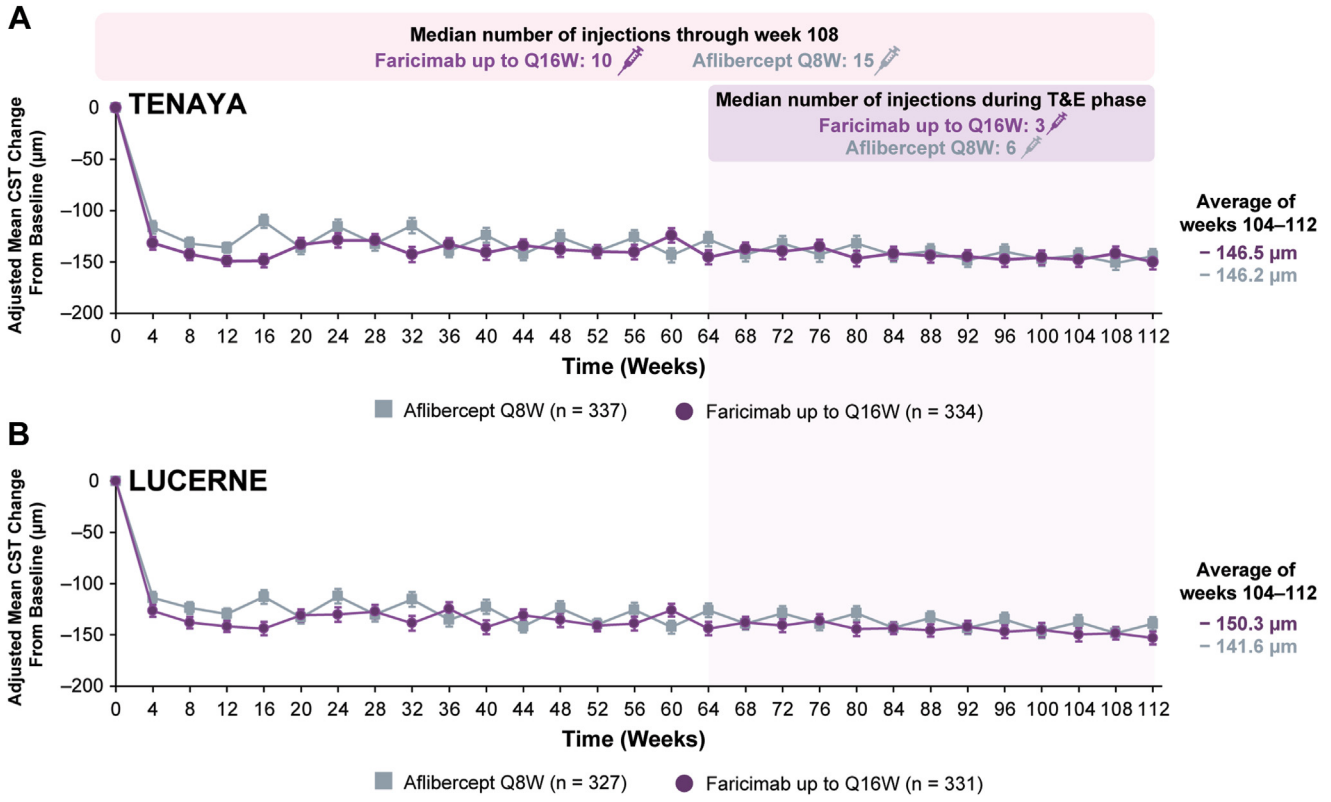

Figure 4. **A**, **B**, Line graphs showing the adjusted mean change in central subfield thickness (CST) from baseline through week 112 of (**A**) TENAYA and (**B**) LUCERNE. Adjusted mean (95.03% confidence interval [CI]) CST change from baseline at 2 years, averaged over weeks 104, 108, and 112. Results are based on a mixed model for repeated measures (MMRM) analysis of the intention-to-treat population. Treatment policy strategy and hypothetical strategy were applied to intercurrent events not related to coronavirus disease 2019 (COVID-19) and related to COVID-19, respectively. Missing data were imputed implicitly by the MMRM. Error bars represent 95.03% CI. Central subfield thickness was defined as the average thickness between the internal limiting membrane and retinal pigment epithelium. Q8W = every 8 weeks; Q16W = every 16 weeks; T&E = treat-and-extend.

aflibercept Q8W, 190 patients [56.5%]) and LUCERNE (faricimab up to Q16W, 175 patients [52.9%]; aflibercept Q8W, 155 patients [47.5%]; Table 5).

In both trials, most ocular AEs were mild or moderate in severity and consistent with what would be expected within an nAMD population treated with intravitreal injections (Table 5). Common ocular AEs reported generally were balanced across treatment arms. The proportion of patients with serious ocular AEs in the study eye through week 112 was low and comparable across study arms in TENAYA (faricimab up to Q16W, 14 patients [4.2%]; aflibercept Q8W, 13 patients [3.9%]) and LUCERNE (faricimab up to Q16W, 15 patients [4.5%]; aflibercept Q8W, 16 patients [4.9%]). A numerically higher number of retinal pigment epithelial tears was observed with faricimab compared with aflibercept in both TENAYA (9 tears [2.7%] and 7 tears [2.1%], respectively) and LUCERNE (10 tears [3.0%] and 3 tears [0.9%], respectively), although they were mostly either mild or moderate in severity (Table S7). Most events occurred during the initial dosing phase, and only 1 epithelial tear was reported in year 2 (aflibercept arm). Nonocular AEs and Anti-Platelet Trialists' Collaboration events also were similar across treatment arms and trials (Table 5).

The incidence of intraocular inflammation (IOI) events through week 112 was low and comparable between patients receiving faricimab up to Q16W (TENAYA, 11 events [3.3%]; LUCERNE, 9 events [2.7%]) and aflibercept Q8W (TENAYA, 5 events [1.5%]; LUCERNE, 10 events [3.1%]; Table 5). All IOI but 5 events were considered by the investigator to be mild or moderate in severity. In TENAYA, 1 case of (recurrent) uveitis occurred in the faricimab arm that was considered by the investigator to be severe and treatment related and led to discontinuation of faricimab. The event was treated with topical corticosteroids and a topical combination ocular hypotensive agent (α_2-adrenergic agonist plus β-blocker) and resolved. In LUCERNE, 2 cases of IOI occurred in the faricimab arm (1 case of uveitis and 1 case of chorioretinitis), and 2 cases of uveitis occurred in the aflibercept arm, all of which were considered by the investigator to be severe. The faricimab uveitis case was considered treatment related and led to faricimab discontinuation. The event was treated with topical corticosteroids (plus a 7-day course of oral corticosteroids) and remained unresolved at week 112. The faricimab chorioretinitis was not considered treatment related and was thought to have a viral cause. Study treatment was withdrawn, and the event was treated with a combination of topical and oral corticosteroids, topical nonsteroidal anti-inflammatory eye drops, and oral antivirals; the event was resolving at week 112. One of the aflibercept uveitis cases was considered treatment related and led to aflibercept discontinuation. This case was treated with topical antibiotics and

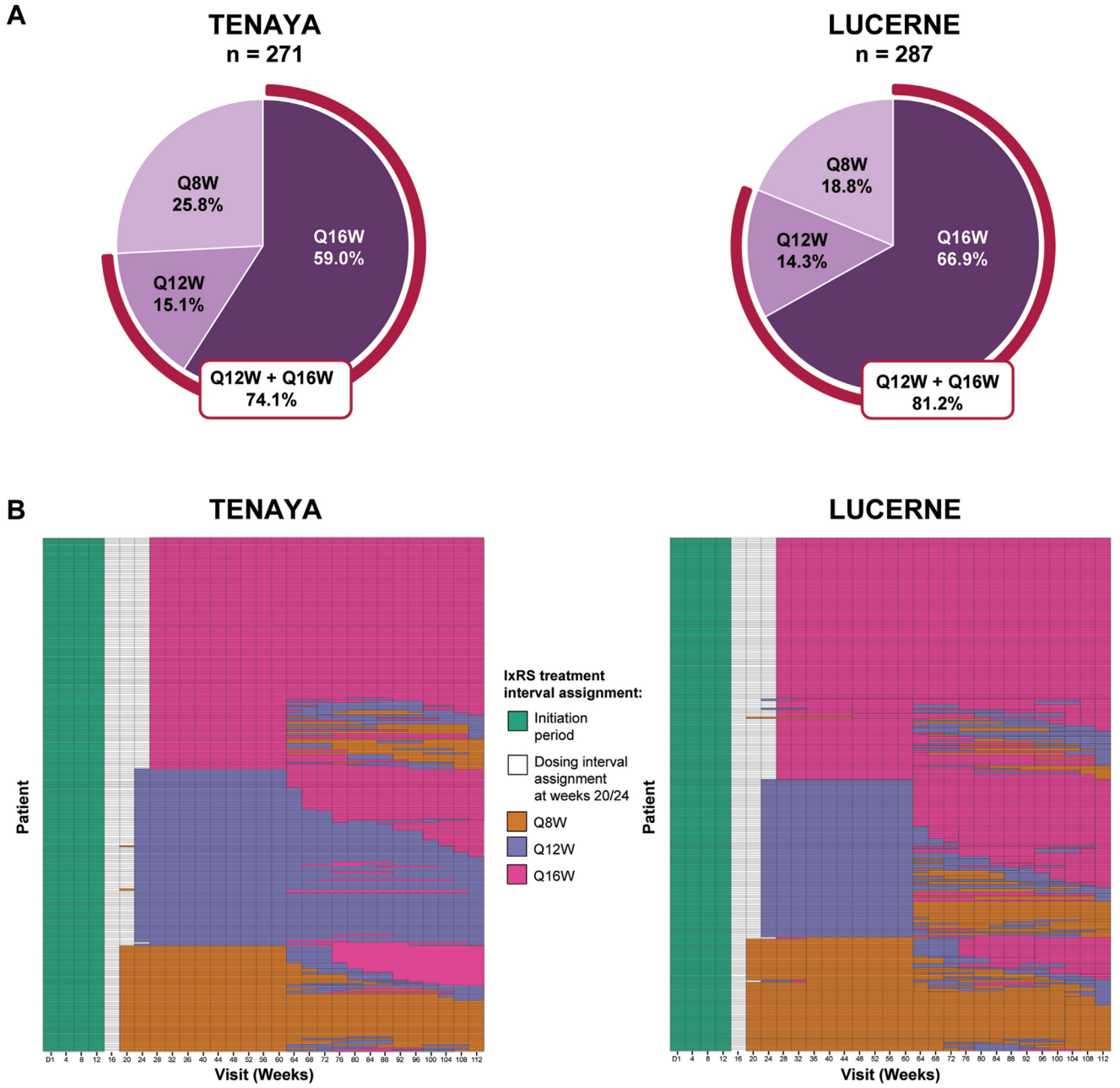

Figure 7. **A**, **B**, Pie graphs showing proportion of patients in the faricimab up to every 16 weeks (Q16W) arms who achieved every 8 weeks (Q8W), every 12 weeks (Q12W), or Q16W dosing at week 112 (**A**), and graphs showing dosing intervals in the faricimab up to Q16W arms through week 112 (**B**). Analyses included patients in the faricimab up to Q16W arms who had not discontinued the study at the week 112 visit (TENAYA, n = 271; LUCERNE, n = 287). Treatment interval at week 112 was defined as the treatment interval decision made using data recorded at week 108 in (**A**), and treatment interval at a given visit is shown as the interval at the start of the visit in (**B**). Red lines in (**A**) indicate the proportion of patients who achieved Q12W or Q16W dosing at week 112. Each horizontal line in (**B**) represents an individual patient over time; the line color represents the dosing interval. The treat-and-extend personalized treatment interval dosing regimen was delayed in some patients because of dose holds or missed visits. D = day; IxRS = interactive voice/web response system. .

corticosteroids and resolved. The second aflibercept case of uveitis was not considered treatment related. As such, the patient continued to receive aflibercept after the event resolved after treatment with topical steroids and intravitreal steroids and antibiotics.

All IOI events except 1 were nonserious. The 1 serious IOI event was the recurrent uveitis in the faricimab arm in TENAYA, which presented during year 1 and was reported in the primary analysis. This event resolved by week 112, although the patient had discontinued faricimab treatment at week 48 after having received 6 intravitreal injections. The patient did not receive any further anti-VEGF treatment after faricimab discontinuation and by week 112 had experienced a sustained

Table 5. Summary of Key Adverse Events through Week 112 (Safety-Evaluable Population)

	TENAYA (n = 669)		LUCERNE (n = 657)	
	Faricimab up to Every 16 Weeks (n = 333)	*Aflibercept Every 8 Weeks (n = 336)*	*Faricimab up to Every 16 Weeks (n = 331)*	*Aflibercept Every 8 Weeks (n = 326)*
Summary of AEs				
Total no. of AEs*	1690	1702	1594	1619
Total no. of SAEs*	139	157	141	223
Patients with ≥ 1 ocular AE†	183 (55.0)	190 (56.5)	175 (52.9)	155 (47.5)
Patients with ≥ 1 ocular SAE†	14 (4.2)	13 (3.9)	15 (4.5)	16 (4.9)
Patients with ≥ 1 nonocular AE	252 (75.7)	245 (72.9)	235 (71.0)	247 (75.8)
Patients with ≥ 1 nonocular SAE	66 (19.8)	76 (22.6)	72 (21.8)	86 (26.4)
Patients with ≥ 1 treatment-related ocular AE†	14 (4.2)	9 (2.7)	12 (3.6)	10 (3.1)
Patients with ≥ 1 treatment-related ocular SAE†	4 (1.2)	0	6 (1.8)	2 (0.6)
Patients with ≥ 1 ocular AE of special interest†‡	12 (3.6)	13 (3.9)	13 (3.9)	14 (4.3)
IOI events†§				
Patients with ≥ 1 IOI event	11 (3.3)	5 (1.5)	9 (2.7)	10 (3.1)
Iritis	5 (1.5)	2 (0.6)	3 (0.9)	1 (0.3)
Uveitis	1 (0.3)	1 (0.3)	3 (0.9)	2 (0.6)
Postprocedural inflammation	0	1 (0.3)	0	4 (1.2)
Vitreitis	3 (0.9)	0	1 (0.3)	1 (0.3)
Iridocyclitis	0	0	2 (0.6)	1 (0.3)
Keratic precipitates	2 (0.6)	0	0	0
Anterior chamber flare	0	1 (0.3)	0	0
Chorioretinitis	0	0	1 (0.3)	0
Noninfectious endophthalmitis	0	0	0	1 (0.3)
Ocular SAEs associated with intravitreal anti-VEGF therapy†‖				
Endophthalmitis	2 (0.6)	0	1 (0.3)	2 (0.6)
Rhegmatogenous retinal detachment	1 (0.3)	0	0	0
Retinal tear	0	1 (0.3)	0	1 (0.3)
Retinal pigment epithelial tear	2 (0.6)	0	2 (0.6)	0
Intraocular pressure increased	0	0	1 (0.3)	1 (0.3)
Traumatic cataract	0	0	1 (0.3)	1 (0.3)
Retinal vasculitis and noninflammatory occlusive events†				
Retinal vasculitis	0	0	0	0
Retinal vein occlusion	0	0	0	0
Retinal artery occlusion	0	0	0	0
Retinal artery embolism	0	0	1 (0.3)¶	0
APTC events#				
Patients with ≥ 1 APTC event	11 (3.3)	9 (2.7)	11 (3.3)	11 (3.4)
Nonfatal myocardial infarction	1 (0.3)	2 (0.6)	2 (0.6)	1 (0.3)
Nonfatal stroke	1 (0.3)	4 (1.2)	3 (0.9)	2 (0.6)
Death	9 (2.7)	3 (0.9)	7 (2.1)	8 (2.5)

AE = adverse event; APTC = Anti-Platelet Trialists' Collaboration; IOI = intraocular inflammation; SAE = serious adverse event.
Data are presented as no. or no. (%). Includes AEs with onset from the first dose of study drug through study end; percentages are based on n values in the column headings. Multiple occurrences of the same AE in 1 individual are counted only once, except for the "Total number of events" rows, in which multiple occurrences of the same AE are counted separately.
*Total number of AEs and SAEs includes nonocular events and ocular events in the study or fellow eye.
†Ocular AEs in the study eye only are presented.
‡Ocular AEs of special interest were defined as events associated with severe IOI, events requiring surgical or medical intervention to prevent permanent loss of sight, or events associated with best-corrected visual acuity loss of ≥ 30 Early Treatment Diabetic Retinopathy Study letters for more than 1 hour. A full list of ocular AEs of special interest is provided in Table S6.
§Includes serious and nonserious IOI events.
‖A full list of ocular SAEs is provided in Table S5.
¶Hollenhorst plaque.
#Adjudicated externally; all other events were investigator reported.

vision loss of 15 letters or more from day 1. No new serious IOI events were reported in the study since the primary analysis. Also, no new retinal vasculitis or noninflammatory occlusive events were reported, in line with their absence at the primary analysis. As previously reported, 1 event of retinal artery embolism (a Hollenhorst plaque) occurred in the faricimab arm of the LUCERNE trial during year 1 that had not resolved by week 112.

Discussion

Year 1 results of TENAYA and LUCERNE demonstrated noninferior visual outcomes with faricimab dosing up to Q16W compared with aflibercept dosing Q8W. These outcomes were achieved with fewer injections for faricimab, with approximately 80% of faricimab-treated patients receiving Q12W or longer dosing and approximately 45% of faricimab-treated patients receiving Q16W dosing at week 48.[9] The 2-year results presented herein build on the year 1 findings demonstrating that visual and anatomic improvements seen with faricimab at year 1 were maintained in year 2. After the transition to the T&E PTI regimen, a treatment regimen that reflects clinical practice as closely as possible, more faricimab-treated patients achieved extended dosing intervals (approximately 80% achieved Q12W or longer dosing and $>$ 60% achieved Q16W dosing). Moving to the T&E regimen during year 2 resulted in significantly fewer injections of faricimab compared with aflibercept Q8W dosing (median, 10 injections vs. 15 injections from baseline through year 2; 3 injections vs. 6 injections during the year 2 T&E phase); however, per the design of the study, aflibercept was given at fixed intervals throughout the 2-year study period.

Despite fewer injections, vision gains achieved with faricimab were comparable with those achieved with aflibercept throughout the 2-year duration of the TENAYA and LUCERNE trials, with a high proportion of patients receiving extended dosing, highlighting the durable efficacy achieved with faricimab treatment. Additional BCVA end points, including the proportion of patients with a BCVA Snellen equivalent of 20/40 or better at 2 years, were comparable across treatment arms, with faricimab-treated patients receiving a median of 3 injections during year 2. Similar to what has been reported in other trials,[14,15] a trend for reduced BCVA gains over time in both treatment arms was observed and in part may be the result of the natural progression of the disease.[16] Patients in TENAYA and LUCERNE showed a higher BCVA at baseline compared with the historical pivotal trials for ranibizumab and aflibercept,[9,15,17,18] reflecting a change in clinical practice to treat patients earlier in the disease course because this is associated with better visual outcomes.[19,20] However, this trend in BCVA that was observed in both arms warrants further investigation. Nonetheless, in both TENAYA and LUCERNE, patients experienced robust and sustained CST reductions in both treatment arms, suggesting that patients achieved good anatomic control over the 2 years.

Clinicians frequently use T&E regimens in clinical practice to deliver personalized care based on an individual patient's disease activity, allowing a reduction in treatment and visit frequency while maintaining good visual outcomes.[21,22] The use of a T&E regimen in year 2 of TENAYA and LUCERNE provided the opportunity to adjust treatment intervals based on disease activity in a manner resembling clinical practice and to assess the durability of faricimab. The T&E regimen in these trials used a comprehensive set of criteria in which any signal suggesting suboptimal efficacy (e.g., loss of visual acuity, reduced anatomic control of fluid, or new macular hemorrhage) would result in a reduction in treatment interval, whereas interval extension was permitted only if disease stability had been observed in both anatomic and functional measures. These criteria were designed to provide the best chance of increasing dosing intervals without impacting efficacy and therefore maintaining BCVA and CST improvements through year 2.

In the faricimab arms, the proportion of patients receiving Q16W dosing in year 2 increased compared with year 1 as patients moved from fixed dosing to T&E dosing. Moreover, most patients who were receiving an extended treatment interval at year 1 were able to maintain the treatment interval through year 2, and therefore, patients received fewer injections of faricimab overall. Furthermore, most patients receiving a more frequent treatment interval during year 1 because of meeting disease activity assessment criteria at weeks 20 and 24 were able to extend to longer intervals during year 2. The results from TENAYA and LUCERNE demonstrate the potential for dual angiopoietin-2 and VEGF-A inhibition with faricimab to extend treatment intervals while maintaining visual gains in patients with nAMD and to address a key unmet need for effective, durable therapies that reduce treatment burden without compromising efficacy outcomes.

The durability of treatment effect with dual angiopoietin-2 and VEGF-A inhibition observed in TENAYA and LUCERNE is supported by preclinical evidence that inhibition of angiopoietin-2 in addition to VEGF-A promotes vascular stability through a reduction in CNV lesion leakage area, neovascularization, and inflammation beyond what can be achieved with anti-VEGF therapy alone.[23,24] In addition to enhanced vascular stability, the extended durability observed with faricimab is in agreement with the sustained suppression of aqueous humor angiopoietin-2 levels of less than baseline through 16 weeks after dosing, whereas VEGF-A levels returned to baseline by 16 weeks after dosing.[25] Furthermore, evidence is insufficient to suggest that increasing the dose of anti-VEGF agent results in improved durability outcomes, because a 4-fold higher anti-VEGF dose administered in the HARBOR and CANDELA trials did not improve durability outcomes further.[26,27] Thus, the extended durability with faricimab likely is driven by the pharmacodynamic effects of dual angiopoietin-2 and VEGF-A inhibition.

Consistent with the year 1 outcomes,[9] faricimab remained well tolerated through study end with an acceptable safety profile. Ocular AEs were comparable across treatment arms and mostly were mild or moderate in severity. The incidence of IOI events was low and comparable across treatment arms through study end.

The long-term safety and tolerability of faricimab will be assessed further in the AVONELLE-X extension study of

patients completing the TENAYA or LUCERNE trials. Faricimab also is being assessed in VOYAGER (ClinicalTrials.gov identifier, NCT05476926), an ongoing observational study following up patients with nAMD or diabetic macular edema for up to 5 years, that will assess anatomic outcomes such as fluid, atrophy, and fibrosis to provide exploratory data and insights on the long-term effects of dual angiopoietin-2 and VEGF-A inhibition.

Strengths of the TENAYA and LUCERNE trials include that they were both large, global, randomized, double-masked, multicenter phase 3 trials evaluating the efficacy, safety, and durability of faricimab over 2 years. That the 2 trials show effectively identical findings over the 2 years is reassuring and supports the robustness of the trial findings. Moreover, the trial design incorporated disease activity criteria to inform dosing decisions, which were standardized yet designed to reflect clinical practice. The standardization of these criteria reduced the possibility of physician bias or variability, which is crucial for achieving analytical reproducibility. Despite being conducted during the COVID-19 pandemic, sensitivity and supplemental analyses in the TENAYA and LUCERNE trials demonstrated the reproducibility of the results and that COVID-19 and any associated protocol deviations had limited effect on the data integrity and study outcomes; no predefined quality tolerance limits were breached in either trial.

Limitations of the phase 3 TENAYA and LUCERNE trials include that as part of the TENAYA and LUCERNE trial designs, patients were required to attend monthly study visits and to receive intravitreal injections of either active treatment or sham to maintain masking, which did not allow for a quality-of-life assessment of the actual active treatment burden on the patients. Additionally, TENAYA and LUCERNE were designed to be registrational trials for faricimab and were noninferiority studies assessing the efficacy of an extended dosing regimen (Q8W, Q12W, and Q16W) of faricimab compared with the globally approved Q8W dosing regimen of aflibercept. Therefore, the trials were not designed to assess the head-to-head durability of faricimab versus aflibercept. Previous studies report that approximately 37% to 60% of patients achieved Q12W or longer dosing and approximately 27% to 46% of patients achieved Q16W dosing after 2 years of aflibercept 2-mg treatment.[28–31]

In conclusion, the phase 3 TENAYA and LUCERNE trials demonstrated that personalized faricimab dosing of up to Q16W based on disease activity can maintain vision gains and control anatomic outcomes through 2 years in patients with nAMD with approximately 80% of patients achieving extended dosing intervals of 12 weeks or more. The durability of treatment effect with faricimab in year 1 was extended further in year 2, with more faricimab-treated patients achieving and maintaining a Q16W dosing regimen, and therefore receiving fewer injections of faricimab in year 2. These data support dual angiopoietin-2 and VEGF-A inhibition with faricimab as a novel approach to target the angiopoietin–Tie2 and VEGF-A pathways involved in nAMD pathogenesis, leading to durable efficacy, giving physicians the potential to extend time between treatments without compromising vision or anatomic outcomes.

Footnotes and Disclosures

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[1] Sierra Eye Associates and the University of Nevada, Reno, School of Medicine, Reno, Nevada.

[2] Roche Products, Ltd., Welwyn Garden City, United Kingdom.

[3] Sydney Retina Clinic, Sydney Eye Hospital, University of Sydney, and Discipline of Surgery, University of New South Wales, Sydney, Australia.

[4] Department of Ophthalmology, Taipei Veterans General Hospital and National Yang Ming Chiao Tung University, Taipei, Taiwan.

[5] Department of Ophthalmology, Peking Union Medical College Hospital, Beijing, China.

[6] Center for Eye Research Australia, Royal Victorian Eye and Ear Hospital, and Department of Surgery, University of Melbourne, Melbourne, Australia.

[7] Ophthalmic Consultants of Boston, Boston, Massachusetts.

[8] Department of Ophthalmology and GRADE Reading Center, University of Bonn, Bonn, Germany.

[9] Department of Ophthalmology, Tokyo Women's Medical University, Tokyo, Japan.

[10] Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois.

[11] Genentech, Inc., South San Francisco, California.

[12] Eye Clinic Zurich West, Zurich, Switzerland.

[13] Department of Ophthalmology, University of Zurich, Zurich, Switzerland.

[14] Department of Ophthalmology, Vienna Reading Center and Ophthalmic Image Analysis Group (OPTIMA), Medical University of Vienna, Vienna, Austria.

[15] Cleveland Clinic Florida, Stuart, Florida.

[16] F. Hoffmann-La Roche Ltd., Mississauga, Ontario, Canada.

[17] Université Paris Cité, AP-HP, Lariboisière, Saint Louis, Fondation Adolphe de Rothschild Hospitals, Paris, France.

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A.K.: Employee – Roche Products Ltd.

A.C.: Consultant – Alcon, Allergan, Apellis, Bayer, Novartis, Roche/Genentech, Inc.; Financial support – Allergan, Bayer, Novartis; Lecturer – Alcon, Allergan, Apellis, Bayer, Nidek, Novartis, Roche/Genentech, Inc.

S.J.C: Consultant – Roche; Lecturer – Allergan, Bayer, Novartis

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J.S.H.: Advisory board – Roche; Board of directors – Ocular Therapeutix; Consultant – 4D Molecular Therapeutics, Adverum, AffaMed, Akouos, Allegro, Allergan, Annexon, Apellis, Applied Genetic Technologies Corporation, AsclepiX, Bionic Vision, DTx, Gemini, Gyroscope, Iveric Bio, Janssen R&D, jCyte, Nanoscope, NGM Bio, Notal Vision, Novartis, Ocuphire, OcuTerra, Palatin, Perceive Biotherapeutics, Ray Therapeutics, Regeneron, Regenxbio, RetinAI, RevOpsis, Roche/Genentech, Inc., Stealth, Thea, Unity, Vanotech, Vinci, Vitranu

F.G.H.: Consultant – 4D Molecular Therapeutics, Alexion, Annexon, Apellis, Bayer, Geuder, Iveric Bio, Janssen, Novartis, Roche/Genentech, Inc.; Financial support – Apellis, Bayer, Bioeq/Formycon, Gyroscope, Iveric Bio, Kanghong, Novartis, Pixium, Roche/Genentech, Inc.; Lecturer – Bayer, Heidelberg Engineering, Novartis, Roche/Genentech, Zeiss; Leadership or fiduciary role – Club Jules Gonin, EURETINA, German Ophthalmological Society

T.I.: Consultant – Bayer, Boehringer Ingelheim, Chugai/Roche, Janssen Pharmaceutical K.K., Kyowa Kirin, Novartis, Senju; Lecturer – Alcon, AMO, Bayer, HOYA, NIDEK, Novartis, Otsuka, Pfizer, Santen, Senju, Topcon; Patents – Topcon; Financial support – Alcon, AMO, HOYA, NIDEK, Novartis, Santen, Senju, Topcon

J.A.I.: Employee – Roche Products Ltd.

J.I.L.: Consultant – Cognition, Eyenuk, *JAMA Ophthalmology* editorial board, Novartis Pharma AG, Roche/Genentech, Inc.; Financial support – Adverum, Aldeyra, Chengdu Kanghong, Graybug, Janssen, NGM Bio, Regeneron, RegenexBio, Roche/Genentech, Inc., Spring Vision, Stealth; Patents – CRC Press/Taylor and Francis; Data safety monitoring board or advisory board – AbbVie, Alimera, Allergan, Aura, Bausch & Lomb, Eyepoint, Iveric Bio, Luxa, Quark, Regeneron, RegenexBio, Santen, Unity, Viridian

H.L.: Employee – Genentech, Inc.

S.M.: Consultant – Bayer (Schweiz) AG, Novartis Pharma Schweiz AG, Roche AG

C.Q.R.: Employee – Genentech, Inc.

U.S.-E.: Consultant – AbbVie, Apellis; Financial support – Apellis, Genentech, Inc., Kodiak, Novartis, RetInSight, Roche; Lecturer – Apellis, Roche

D.S.: Employee – Roche Products, Ltd.

R.S.: Consultant – Alcon, AsclepiX, Bausch & Lomb, Genentech, Inc., Gyroscope, Novartis, Regeneron

B.S.: Employee – F. Hoffmann-La Roche Ltd. (at the time of the study)

J.R.W.: Employee – Genentech, Inc.

R.T.: Consultant – AbbVie, Alcon, Allergan, Apellis, Bayer, Genentech, Inc., Iveric Bio, KHB, Oculis, OcuTerra, Roche, Thea; Lecturer – Alcon, Bayer, Genentech, Inc., KHB, Novartis, Oculis, Roche, Zeiss; Financial support – Bayer, Novartis; Equity owner – Oculis; Nonfinancial support – Zeiss

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Author Contributions:

Conception and design: Kotecha, Lin, Quezada Ruiz, Silverman, Swaminathan

Analysis and interpretation: Khanani, Kotecha, Chang, S.-J.Chen, Y.Chen, Guymer, Heier, Holz, Iida, Ives, Lim, Lin, Michels, Quezada Ruiz, Schmidt-Erfurth, Silverman, Singh, Swaminathan, Willis, Tadayoni

Data collection: Khanani, Kotecha, Chang, S.-J.Chen, Y.Chen, Guymer, Heier, Holz, Iida, Ives, Lim, Lin, Michels, Quezada Ruiz, Schmidt-Erfurth, Silverman, Singh, Swaminathan, Willis, Tadayoni

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Overall responsibility: Khanani, Kotecha, Chang, S.-J.Chen, Y.Chen, Guymer, Heier, Holz, Iida, Ives, Lim, Lin, Michels, Quezada Ruiz, Schmidt-Erfurth, Silverman, Singh, Swaminathan, Willis, Tadayoni

Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval;

CNV = choroidal neovascularization; **COVID-19** = coronavirus disease 2019; **CST** = central subfield thickness; **IOI** = intraocular inflammation; **nAMD** = neovascular age-related macular degeneration; **PTI** = personalized treatment interval; **Q8W** = every 8 weeks; **Q12W** = every 12 weeks; **Q16W** = every 16 weeks; **SD** = standard deviation; **T&E** = treat-and-extend.

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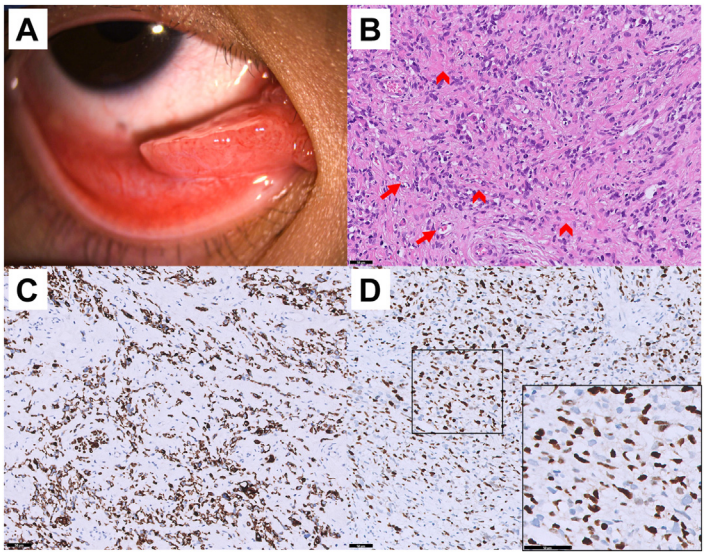
Correspondence:
Arshad M. Khanani, MD, MA, 950 Ryland Street, Reno, Nevada 89511. E-mail: arshad.khanani@gmail.com.

References

1. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392:1147−1159.
2. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106−e116.
3. Swaroop A, Chew EY, Rickman CB, Abecasis GR. Unraveling a multifactorial late-onset disease: from genetic susceptibility to disease mechanisms for age-related macular degeneration. *Annu Rev Genomics Hum Genet*. 2009;10:19−43.
4. Adamis AP, Brittain CJ, Dandekar A, Hopkins JJ. Building on the success of anti-vascular endothelial growth factor therapy: a vision for the next decade. *Eye (Lond)*. 2020;34:1966−1972.
5. Joussen AM, Ricci F, Paris LP, et al. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye (Lond)*. 2021;35:1305−1316.
6. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*. 2017;16:635−661.
7. Khanani AM, Russell MW, Aziz AA, et al. Angiopoietins as potential targets in management of retinal disease. *Clin Ophthalmol*. 2021;15:3747−3755.
8. Khan M, Aziz AA, Shafi NA, et al. Targeting angiopoietin in retinal vascular diseases: a literature review and summary of clinical trials involving faricimab. *Cells*. 2020;9:1869.
9. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399:729−740.
10. Querques G, London N, Kotecha A, et al. Faricimab rapidly improves fluid parameters in patients with nAMD. *Invest Ophthalmol Vis Sci*. 2023;64:2185−2185.
11. Wykoff CC, Abreu F, Adamis AP, et al. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. *Lancet*. 2022;399:741−755.
12. Genentech, Inc. Vabsymo™ (faricimab-svoa) prescribing information. 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761235s0011bl.pdf. Accessed March 14, 2023.
13. Khanani AM, Guymer RH, Basu K, et al. TENAYA and LUCERNE: rationale and design for the phase 3 clinical trials of faricimab for neovascular age-related macular degeneration. *Ophthalmol Sci*. 2021;1:100076.
14. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;128:89−99.
15. 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;121:193−201.
16. Cohen SY, Oubraham H, Uzzan J, et al. Causes of unsuccessful ranibizumab treatment in exudative age-related macular degeneration in clinical settings. *Retina*. 2012;32:1480−1485.
17. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1432−1444.
18. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355:1419−1431.
19. Rasmussen A, Brandi S, Fuchs J, et al. Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. *Acta Ophthalmol*. 2015;93:616−620.
20. Gillies MC, Campain A, Barthelmes D, et al. Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. *Ophthalmology*. 2015;122:1837−1845.
21. American Academy of Ophthalmology. Age-related macular degeneration Preferred Practice Pattern. 2019. https://www.aao.org/Assets/12aabf44-f548−429f-84a5-ace87e6620c9/637841637085900000/age-related-macular-degeneration-ppp-2022-update-pdf. Accessed March 14, 2023.
22. Daien V, Finger RP, Talks JS, et al. Evolution of treatment paradigms in neovascular age-related macular degeneration: a review of real-world evidence. *Br J Ophthalmol*. 2021;105:1475−1479.
23. 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;8:1265−1288.
24. 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:e10666. Available at: https://www.embopress.org/doi/full/10.15252/emmm.201910666.
25. Bogman K, Avery R, Stoilov I, Diack C. Faricimab causes rapid and sustained intraocular suppression of Ang-2 and VEGF-A for up to 16 weeks in nAMD and DME. *Invest Ophthalmol Vis Sci*. 2023;64:2633−2633.
26. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:2181−2192.
27. Wykoff CC, Brown DM, Reed K, et al. Effect of high-dose intravitreal aflibercept, 8 mg, in patients with neovascular age-related macular degeneration: the phase 2 CANDELA randomized clinical trial. *JAMA Ophthalmol*. 2023;141:834−842.
28. Ohji M, Takahashi K, Okada AA, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR: a randomized controlled trial. *Adv Ther*. 2020;37:1173−1187.

29. Mitchell P, Holz FG, Hykin P, et al. Efficacy and safety of intravitreal aflibercept using a treat-and-extend regimen for neovascular age-related macular degeneration: the ARIES study: a randomized clinical trial. *Retina*. 2021;41:1911–1920.
30. Ebneter A, Michels S, Pruente C, et al. Two-year outcomes of intravitreal aflibercept in a Swiss routine treat and extend regimen for patients with neovascular age-related macular degeneration. *Sci Rep*. 2020;10:20256.
31. Singh RP, Yu JS, Guruprasad B, Agashivala N. Anti-VEGF treatment patterns in patients with wet age-related macular degeneration in clinical practice. *Ophthalmic Surg Lasers Imaging Retina*. 2021;52:263–272.

Pictures & Perspectives



Conjunctival Spindle Cell/Sclerosing Rhabdomyosarcoma

A 13-year-old Asian boy had a fast-growing solid mass on his right lower palpebral conjunctiva and medial canthus for 1 month (**A**). Magnetic resonance imaging revealed 2 masses in the medial and inferior orbit. Histopathology of the conjunctival tumor showed ovoid and spindled cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm, arranged in a fascicular pattern within hyalinized stroma (arrowheads). Some exhibited a pseudovascular pattern (**B,** arrows). Immunohistochemical staining results were positive for desman (**C**) and MyoD1 (**D**). Molecular analysis revealed an absence of the *PAX3/FOXO1* fusion gene. The boy was diagnosed with spindle cell/sclerosing rhabdomyosarcoma and received concurrent chemotherapy. (Magnified version of Figure **A**-**D** is available online at www.aaojournal.org).

Yi-Wen Su, MD[1]
Lei-Chi Wang, MD, PhD[2,3]
Nai-Wen Fan, MD, PhD[1,3]

[1]*Department of Ophthalmology, Taipei Veterans General Hospital, Taipei, Taiwan;* [2]*Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;* [3]*School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan*