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Intravitreal Aflibercept 8 mg in Neovascular Age-Related Macular Degeneration

Ninety-Six-Week Results from the Randomized Phase 3 PULSAR Trial

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Purpose: To report the efficacy, durability, and safety of intravitreal aflibercept 8 mg versus intravitreal aflibercept 2 mg every 8 weeks (2q8) in patients with neovascular age-related macular degeneration (nAMD) through 96 weeks, PULSAR (ClinicalTrials.gov identifier, NCT04423718).

Design: Phase 3, randomized, noninferiority, 96-week trial.

Participants: Treatment-naive adults ≥ 50 years with nAMD.

Methods: Patients were randomized 1:1:1 to intravitreal aflibercept 8 mg every 12 or 16 weeks (8q12 or 8q16), or 2q8, after 3 initial monthly doses; dosing intervals in 8-mg groups were modified based on prespecified criteria.

Main Outcome Measures: Change from baseline in best-corrected visual acuity (BCVA) and central retinal thickness (CRT), proportion of patients maintaining or extending the randomized dosing intervals, and safety outcomes.

Results: Of 1009 patients treated, 869 patients (8q12, n = 291; 8q16, n = 292; 2q8, n = 286) completed treatment through week 96. Least squares (LS) mean change from baseline in BCVA at week 96 was +5.6 (95% confidence interval [CI], 4.1–7.1), +5.5 (95% CI, 4.0–7.0), and +6.6 (95% CI, 5.2–8.0) letters in the 8q12, 8q16, and 2q8 groups, respectively; 8q12 and 8q16 differences versus 2q8 in LS mean BCVA changes at week 96 met the noninferiority criteria specified for the primary end point at week 48. Mean (standard deviation) change in CRT from baseline was −143.9 (123.6) μm, −153.4 (140.8) μm, and −135.8 (133.1) μm in the 8q12, 8q16, and 2q8 groups, respectively. Patients completing 96 weeks of treatment in the 8q12, 8q16, and 2q8 groups received a mean of 9.7, 8.2, and 12.8 active injections, respectively. Of these, 87% of patients in the 8q12 group had last assigned dosing intervals of 12 weeks or more, whereas 78%, 53%, and 31% of patients in the 8q16 group qualified for last assigned dosing intervals of ≥ 16 weeks, ≥ 20 weeks, and 24 weeks, respectively. Incidence of ocular treatment-emergent adverse events was similar across groups.

Conclusions: Aflibercept 8 mg delivered sustained disease control in patients with nAMD, maintaining improvements in visual and anatomic outcomes through week 96 with extended dosing intervals and similar safety profile to aflibercept 2 mg.

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Age-related macular degeneration (AMD) is a leading cause of blindness in older adults and is predicted to affect up to 288 million adults in 2040.[1] The wet form of AMD, or neovascular AMD (nAMD), accounts for approximately 10% to 20% of all cases of AMD, but is responsible for nearly 90% of severe vision loss resulting from AMD.[2] The advent of therapies targeting vascular endothelial growth factor (VEGF) has transformed the management

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of nAMD, resulting in significant improvements in visual and anatomic outcomes in landmark clinical trials in nAMD.[3–7] However, although rapid functional and anatomic improvements are evident in the first year of treatment in the clinical setting, a loss in initial visual gains often is observed over time; this likely results from the natural progression of the disease, suboptimal treatment or undertreatment resulting from the challenging treatment burden, including the need for regular frequent injections and clinic visits.[7–12] The consequent burden on patients, caregivers, physicians, and health care systems has resulted in efforts to extend dosing intervals (e.g., treat-and-extend regimens) with varying outcomes.[5,13–15]

The efficacy and safety of the intravitreal anti-VEGF agent aflibercept 2 mg is well documented, and aflibercept 2 mg is approved for the treatment of nAMD in many countries worldwide.[7] To address the need to reduce treatment burden while maintaining visual benefits, an 8-mg formulation of aflibercept was developed to enable the intravitreal delivery of a 4-times higher molar dose compared with the 2-mg formulation.[16] The efficacy and safety of aflibercept 8 mg in nAMD were evaluated in the phase 3 PULSAR trial.[17] The study met its primary efficacy end point, demonstrating the noninferiority of intravitreal aflibercept 8 mg every 12 weeks (8q12) and intravitreal aflibercept 8 mg every 16 weeks (8q16) versus aflibercept 2 mg every 8 weeks (2q8), each after 3 monthly doses, with respect to visual acuity gains at week 48. Aflibercept 8 mg also was superior to aflibercept 2 mg in terms of the key secondary end point, the proportion of patients without retinal fluid at week 16, the time point at which all treatment groups had an interval of 8 weeks since the last initial monthly injection. These improvements in fluid control were maintained through week 48. During the first 48 weeks of the PULSAR trial, patients in the aflibercept 8-mg groups could have the dosing intervals shortened if prespecified dose regimen modification (DRM) criteria were met. Despite multiple time points through week 48 at which the dosing interval could be shortened, 83% of patients who completed 48 weeks of treatment with aflibercept 8 mg maintained their randomized dosing intervals of 12 or 16 weeks.[17] The safety profile of aflibercept 8 mg was similar to that of aflibercept 2 mg, with no new safety concerns identified.[17] These results supported the regulatory approval of aflibercept 8 mg for the treatment of nAMD across Europe and in the United States and Japan.[18–20]

Herein, we present results from the PULSAR trial reporting the efficacy and safety of aflibercept 8 mg versus aflibercept 2 mg in patients with nAMD through week 96. Of note, beginning at week 52, patients receiving aflibercept 8 mg could have had their dosing intervals extended based on DRM criteria, with a maximum possible assigned dosing interval of every 24 weeks. The results of this study addressed the following key clinical questions: whether the initial improvements at 48 weeks with aflibercept 8 mg were maintained through 96 weeks, whether longer dosing intervals beyond 16 weeks (and thus fewer injections) were feasible, and whether any new safety signals were detected through 96 weeks that were not observed during the first 48 weeks.

Methods

Study Design

The PULSAR trial (ClinicalTrials.gov identifier, NCT04423718) was a randomized, double-masked, active-controlled, 96-week, noninferiority phase 3 trial evaluating the efficacy and safety of aflibercept 8 mg compared with aflibercept 2 mg in patients with treatment-naive nAMD.[17] The trial was conducted in 223 clinical sites across 27 countries in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, and applicable local laws and regulations. The protocol was reviewed and approved by the relevant institutional review boards and independent ethics committees (as listed in the Appendix, available at www.aaojournal.org) before the trial was initiated. All patients provided written informed consent before participating in the trial.

Details of the inclusion and exclusion criteria for the PULSAR trial have been described previously.[17] Treatment-naïve adults $\geq$ 50 years with nAMD were eligible, with 1 eye per patient designated as the study eye. Active, subfoveal choroidal neovascularization secondary to nAMD (including juxtafoveal lesions that affect the fovea), best-corrected visual acuity (BCVA) of 78 to 24 Early Treatment Diabetic Retinopathy Study letters (Snellen equivalent, approximately 20/32–20/320), and total choroidal neovascularization area (including both classic and occult components) of >50% of the total lesion area were required in the study eye. Intraretinal fluid, subretinal fluid, or both affecting the center subfield of the study eye must have been observed on spectral-domain (SD)-OCT. Exclusion criteria included total lesion size of > 12 disc areas (30.5 mm^2) in the study eye.

Randomization and masking have been described previously.[17] Eligible patients were assigned randomly in a 1:1:1 ratio to 1 of 3 parallel treatment groups: 2q8, 8q12, or 8q16, each after 3 initial monthly doses (Fig S1, available at www.aaojournal.org). Aflibercept 2-mg and 8-mg doses were administered at concentrations of 40 mg/ml and 114.3 mg/ml using injection volumes of 0.05 ml and 0.07 ml, respectively. Patients in the 8q12 and 8q16 groups received either sham injections or active study treatment at all visits through week 92, depending on the assigned treatment group and eligibility for DRM (for 8q12 and 8q16 groups). Beginning at week 16, patients in the 8q12 and 8q16 groups were assessed and the dosing interval was shortened if the following DRM criteria were met: (1) BCVA loss of > 5 letters from week 12 and (2) either a > 25-μm increase in central retinal thickness (CRT) from week 12 or new foveal hemorrhage or new foveal neovascularization.[17] Visits were scheduled at screening, baseline (day 1), and every 4 weeks through week 96.

Beginning at week 52, patients receiving aflibercept 8 mg were eligible for dosing interval extension based on prespecified DRM criteria (Fig S1). Dosing intervals were extended by 4-week increments if all of the following DRM criteria were met at a dosing visit: BCVA loss of < 5 letters compared with week 12, no fluid in the center subfield on SD-OCT, and no new-onset foveal hemorrhage or foveal neovascularization. Because of the study design and duration of 96 weeks, the maximum completed dosing interval was 20 weeks and the maximum assigned dosing interval was 24 weeks for patients receiving aflibercept 8 mg.

Procedures

Key assessments conducted at each visit included BCVA (measured by Early Treatment Diabetic Retinopathy Study letter score), indirect ophthalmoscopy, SD-OCT, and intraocular pressure (IOP), as previously described.[17] Central retinal thickness and the presence of fluid were assessed using SD-OCT. Intraocular pressure was measured before injection bilaterally at all visits using the same method for each patient throughout the trial. At dosing visits, IOP also was required to be measured approximately 30 to 60 minutes after injection in the study eye. All personnel who evaluated efficacy, including BCVA examiners, were masked to treatment assignment. Furthermore, images obtained via SD-OCT, fluorescein angiography, and fundus photography were obtained by masked personnel and were assessed by masked graders at an independent central reading center. Fluorescein angiography was performed at screening and weeks 12, 24, 36, 48, 60, and 96 to confirm nAMD diagnosis and monitor response to treatment throughout the trial.

Outcome Measures

The primary end point, change from baseline in BCVA at week 48, and the key secondary efficacy end point, absence of fluid at week 16, were reported previously.[17] Prespecified efficacy end points at week 96 were exploratory and included change from baseline in BCVA and CRT and the proportion of participants with no fluid (defined as no intraretinal fluid and no subretinal fluid) in the center subfield. The proportion of patients who maintained or extended their randomized dosing intervals through week 96 also was assessed as an exploratory end point. Safety end points included the incidence of ocular and nonocular treatment-emergent adverse events (TEAEs) through week 96.

Statistical Analysis

The analyses for efficacy and safety end points at week 96 were conducted using the same statistical methods as described in the primary analysis publication.[17] All efficacy analyses were conducted in the full analysis set (FAS), which comprised all randomized patients who received at least 1 dose of study treatment according to original randomization. Exploratory efficacy end points at week 96 were analyzed descriptively, and only nominal *P* values are provided for treatment comparisons.

An estimand that was based on a hypothetical strategy was used for analyses at week 96, consistent with analyses performed at week 48. The change from baseline in BCVA measured by Early Treatment Diabetic Retinopathy Study letter score at week 96 was summarized by treatment group for all observed cases. Differences in least squares (LS) mean change from baseline to week 96 in BCVA between the 8q12 and 2q8 groups and between the 8q16 and 2q8 groups (along with corresponding 95% confidence intervals [CIs]) were calculated using a mixed model for repeated measures (MMRM) with baseline BCVA measurement as covariate and treatment group, visit, and stratification variables as fixed factors as well as terms for the interaction between baseline and visit and for the interaction between treatment and visit. A similar MMRM was used to calculate the difference in LS mean change in CRT from baseline, using baseline CRT instead of baseline BCVA values. To model the within-subject error, the Toeplitz heterogeneity covariance structure was used. In accordance with the hypothetical estimand strategy that was applied to the primary end point at week 48,[17] BCVA and CRT data after the first occurrence of relevant intercurrent events were excluded. Missing or excluded data were handled implicitly by the MMRM. A sensitivity analysis (analysis of covariance) of change from baseline in BCVA at week 96 was conducted using data with the last observation after baseline carried forward.

The proportion of participants without retinal fluid in the center subfield at week 96 was analyzed descriptively. Data after the first occurrence of relevant intercurrent events were excluded. Missing or excluded data were imputed using the last observation carried forward approach.

Safety outcomes were assessed in the safety analysis set, which included all randomized patients who received study treatment, and were presented by actual treatment received. Ocular and nonocular TEAEs were reported and coded using the Medical Dictionary for Regulatory Activities version 26.0. An independent data monitoring committee provided safety monitoring throughout the trial, and an independent Anti-Platelet Trialists' Collaboration adjudication committee evaluated all potential events according to a prespecified and agreed-on charter. Statistical analyses were performed using the software package SAS version 9.4 or higher (SAS Institute, Inc.).

Results

Patient Disposition

In total, 1009 patients were assigned randomly and were treated with aflibercept 8 mg or 2 mg at baseline (8q12, n = 335; 8q16, n = 338; 2q8, n = 336; Fig 2). Of these, 869 patients (86.1%) completed treatment through week 96 (8q12, n = 291 [86.9%]; 8q16, n = 292 [86.4%]; 2q8, n = 286 [85.1%]). Important protocol deviations were reported in 345 patients (34.1%), and the proportion of patients with important protocol deviations was comparable across treatment groups (Table S1, available at www.aaojournal.org). The most common important protocol deviations were treatment deviations for 2q8, procedural deviations for 8q12, and time schedule deviations (most because of coronavirus disease 2019 pandemic-related logistical reasons) for 8q16.

Baseline Characteristics and Aflibercept Exposure

As reported previously, baseline demographic and disease characteristics generally were well balanced across treatment groups.[17] Patients who completed week 96 in the 8q12, 8q16, and 2q8 groups received a mean of 9.7, 8.2, and 12.8 active injections, respectively, through week 96 and 3.7, 3.0, and 5.8 injections, respectively, from weeks 48 through 96.

Efficacy Outcomes

Visual gains achieved at week 48 were maintained through week 96 in the 8q12, 8q16, and 2q8 groups (Fig 3). The arithmetic mean (standard deviation) change from baseline in BCVA at week 96 was +5.9 (14.2) letters, +5.6 (13.7) letters, and +7.4 (13.8) letters in the 8q12, 8q16, and 2q8 groups, respectively (Fig 3A). The LS mean change from baseline in BCVA at week 96 was +5.6 letters (95% CI, 4.1−7.1 letters), +5.5 letters (95% CI, 4.0−7.0 letters), and +6.6 letters (95% CI, 5.2−8.0 letters) in the 8q12, 8q16, and 2q8 groups, respectively (Fig 3B). The difference in LS mean change

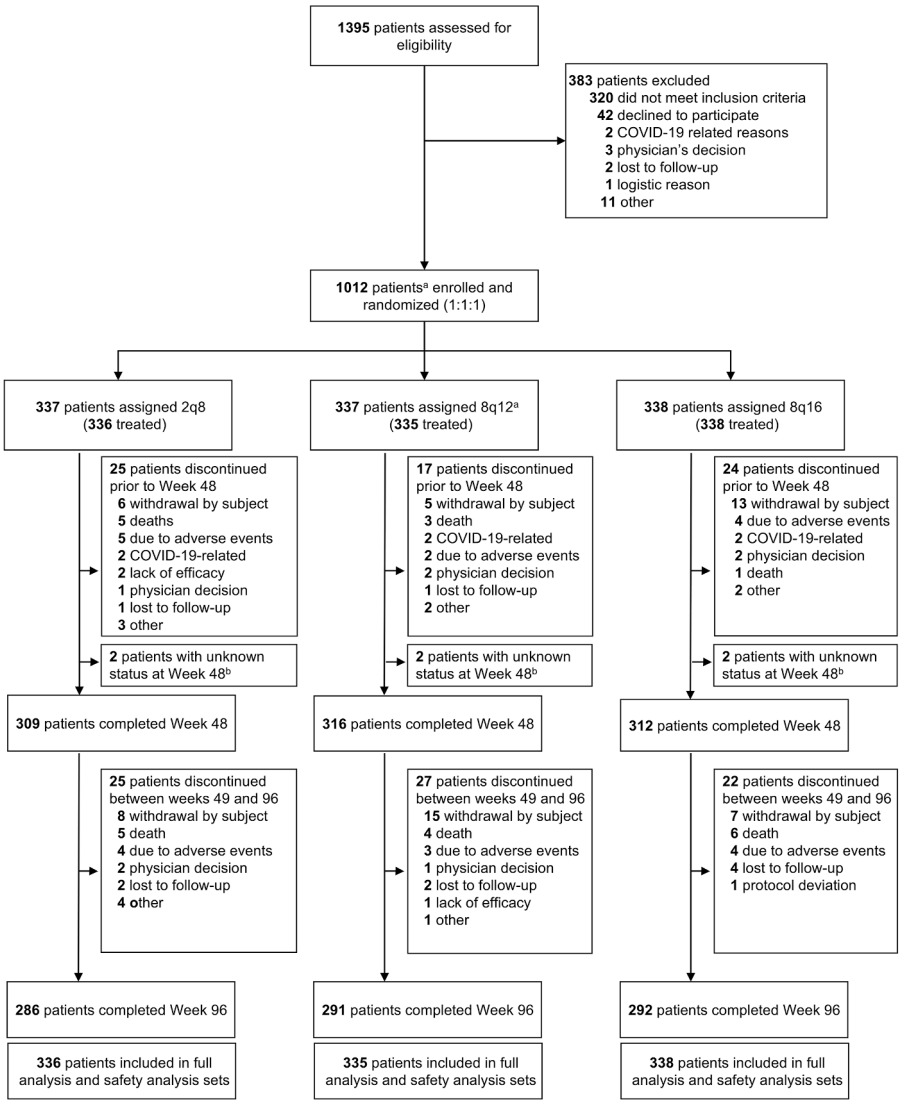
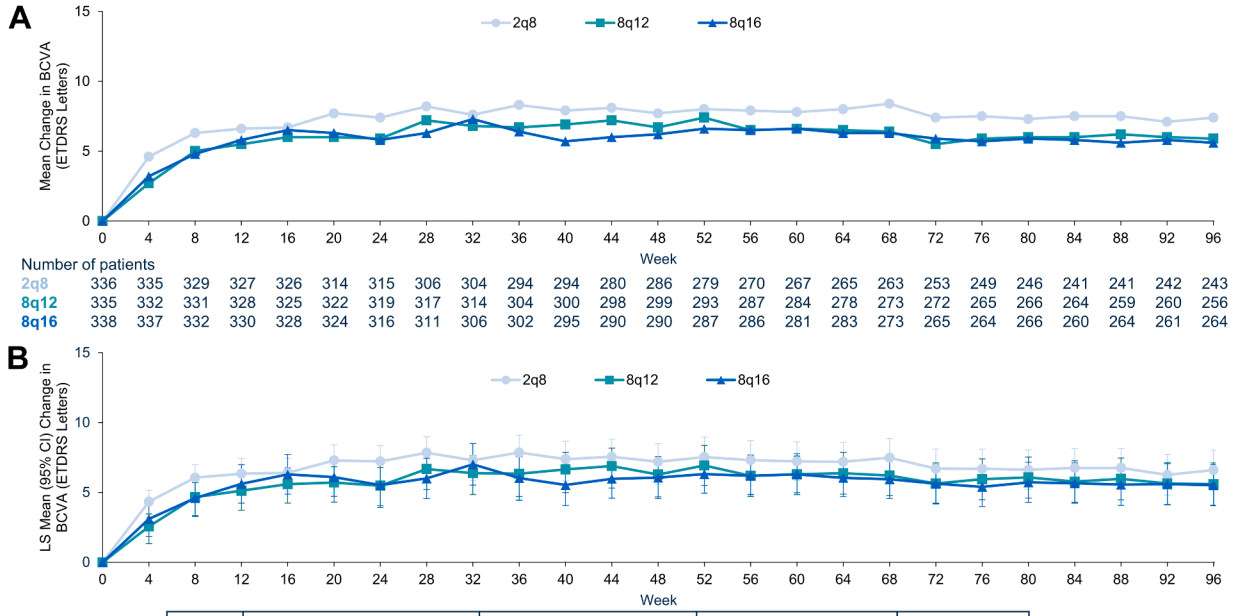


Figure 2. Flow diagram showing patient disposition through week 96 of the PULSAR trial. [a]One patient was assigned randomly in error, although they did not complete screening and had withdrawn consent. This individual was included in the number of patients randomized in the week 96 database, but not in the number of patients randomized in the previously reported week 48 database.[17] [b]Overall, 6 patients had missing week 48 information (i.e., they neither discontinued during the week 48 time frame, nor had the week 48 visit performed or marked as not done). These patients were considered to have continued in the study to week 96. COVID-19 = coronavirus disease 2019; 8q16 = aflibercept 8 mg every 16 weeks; 8q12 = aflibercept 8 mg every 12 weeks; 2q8 = aflibercept 2 mg every 8 weeks.

from baseline to week 96 in BCVA was −1.01 letters (95% CI, −2.82 to 0.80 letters) between 8q12 and 2q8 groups and −1.08 letters (95% CI, −2.87 to 0.71 letters) between 8q16 and 2q8 groups. These outcomes at week 96 met the noninferiority criteria that had been specified for the primary end point at week 48 (i.e., the lower limit of the 95% CI did not exceed the noninferiority margin of 4 letters; nominal P value of 1-sided test for noninferiority at a margin of 4 letters, 8q12 vs. 2q8: $P = 0.0006$; 8q16 vs 2q8: $P = 0.0007$). Findings from the sensitivity analysis were consistent with those of the main efficacy analysis using MMRM in the FAS (Table S2, available at www.aaojournal.org).

At week 96, the proportion of patients with no retinal fluid in the center subfield was 69.6% (231/332) in the 8q12 group, 63.6% (213/335) in the 8q16 group, and 66.5% (222/334) in the 2q8 group (Fig 4). The arithmetic mean (standard deviation) change from baseline in CRT at week 96 was −143.9 (123.6) μm, −153.4 (140.8) μm, and −135.8 (133.1) μm in the 8q12, 8q16, and 2q8 groups, respectively (Fig 5A). The LS mean change from baseline in CRT at week 96 was −152.0 μm (95% CI, −159.4 to −144.5 μm), −148.8 μm (95% CI, −156.0 to −141.6) μm, and −146.8 μm (95% CI, −154.1 to −139.5 μm) in the aflibercept 8q12, 8q16, and 2q8 groups, respectively (Fig 5B).



	Arithmetic mean change from baseline at Week 96	LS mean change from baseline at Week 96	Difference in LS means versus 2q8	Two-sided 95% CI
2q8	7.4	6.6	–	–
8q12	5.9	5.6	–1.01	–2.82 to 0.80
8q16	5.6	5.5	–1.08	–2.87 to 0.71

Figure 3. Graphs showing arithmetic mean change (**A**) and least squares (LS) mean change (**B**) from baseline in best-corrected visual acuity (BCVA) through week 96. **A,** Arithmetic mean change from baseline in BCVA is based on observed data before intercurrent events (ICEs). The number of patients included in the analysis, excluding patients with relevant ICEs, was provided for each time point. **B,** The LS mean change from baseline in BCVA was generated using a mixed model for repeated measures (MMRM), with baseline BCVA as a covariate, treatment group (intravitreal aflibercept 2 mg every 8 weeks [2q8], intravitreal aflibercept 8 mg every 12 weeks [8q12], and intravitreal aflibercept 8 mg every 16 weeks [8q16]) and stratification variables (geographic region [Japan vs. rest of the world] and baseline BCVA [<60 versus ≥60 Early Treatment Diabetic Retinopathy Study (ETDRS) letters]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. Missing data were covered by the MMRM. Full analysis set. CI = confidence interval.

Durability Outcomes

Figure 6 displays the dosing intervals for patients in the aflibercept 8-mg treatment groups who completed treatment through week 96 (8q12, n = 291; 8q16, n = 292; combined 8 mg, n = 583). Overall, 219 patients (75%) in the 8q12 group and 205 patients (70%) in the 8q16 group maintained their randomized dosing interval or qualified for further dosing interval extension through week 96, respectively (Fig 6A).

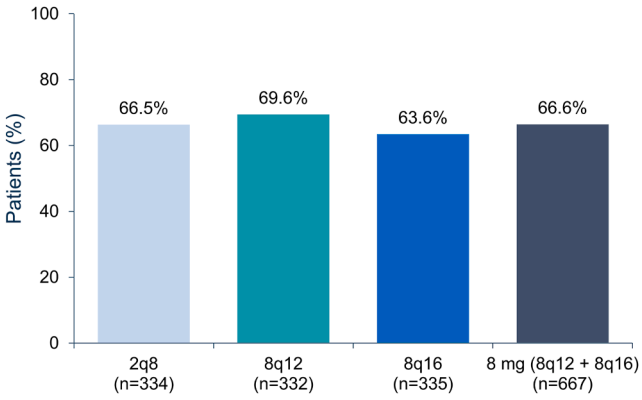


Figure 4. Bar graph showing proportions of patients without retinal fluid in the center subfield at week 96, full analysis set, last observation carried forward (censoring data after intercurrent event). The absence of retinal fluid was defined as no intraretinal fluid and no subretinal fluid in the center subfield. 8q16 = aflibercept 8 mg every 16 weeks; 8q12 = aflibercept 8 mg every 12 weeks; 2q8 = aflibercept 2 mg every 8 weeks.

At week 96, 252 patients (87%) in the 8q12 group and 230 patients (79%) in the 8q16 group had a last completed dosing interval of ≥ 12 weeks and ≥ 16 weeks, respectively (Fig 6B). Furthermore, 90 patients (31%) and 141 patients (48%) in the 8q12 and 8q16 groups, respectively, completed a 20-week dosing interval by week 96. Overall, 118 patients (41%) and 155 patients (53%) in the 8q12 and 8q16 groups, respectively (273 patients [47%] in the combined 8-mg group), qualified for a last assigned dosing interval of ≥ 20 weeks, with 72 patients (25%) and 90 patients (31%), respectively (162 patients [28%] in the combined 8-mg group), qualifying for a last assigned dosing interval of 24 weeks.

Safety Outcomes

Ocular TEAEs in the study eye were reported in 171 patients (51.0%), 174 patients (51.5%), and 181 patients (53.9%) in the 8q12, 8q16, and 2q8 groups, respectively,

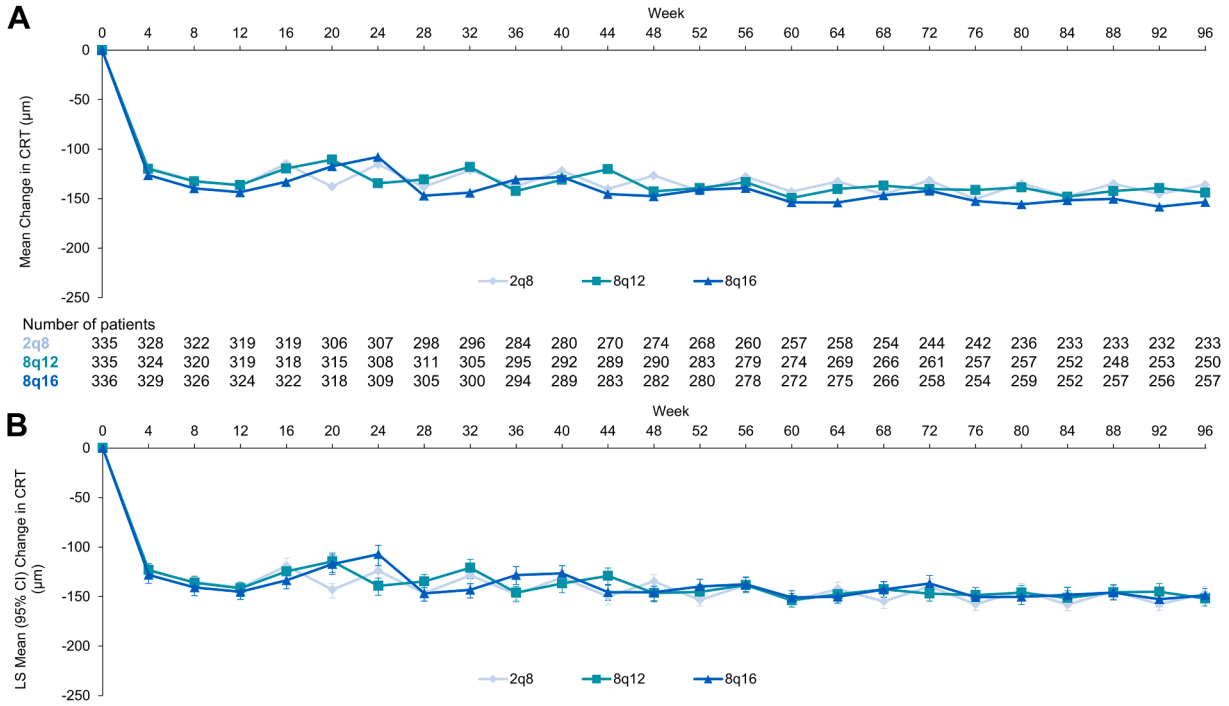


Figure 5. Graphs showing arithmetic mean change (**A**) and least squares (LS) mean change (**B**) from baseline in central retinal thickness (CRT) through week 96. **A,** Arithmetic mean change from baseline in CRT was based on observed data before intercurrent events. **B,** The LS mean change from baseline in CRT was generated using a mixed model for repeated measures, with baseline CRT as a covariate, treatment group (intravitreal aflibercept 2 mg every 8 weeks [2q8], intravitreal aflibercept 8 mg every 12 weeks [8q12], and intravitreal aflibercept 8 mg every 16 weeks [8q16]) and stratification variables (geographic region [Japan vs. rest of the world] and baseline best-corrected visual acuity [<60 Early Treatment Diabetic Retinopathy Study (ETDRS) letters vs. ≥ 60 ETDRS letters]) as fixed factors, and terms for the interaction between baseline CRT and visit and the interaction between treatment and visit. Full analysis set.

through week 96 (Table 3). The most common ocular TEAEs in the 8q12, 8q16, and 2q8 groups were cataract (9.6%−10.1% across groups), reduced visual acuity (6.3%−7.1% across groups), and retinal hemorrhage (5.4%−5.7% across groups; Table S4, available at www.aaojournal.org). Serious ocular TEAEs in the study eye were reported in 24 patients (2.4%; Table 3) and included retinal detachment, retinal hemorrhage, cataract, increased IOP, angle-closure glaucoma, dry AMD, macular detachment, skin laceration, vitreous hemorrhage, retinal tear, and endophthalmitis. One serious ocular TEAE of angle-closure glaucoma was reported in a patient from the 8q16 group with a medical history of angle-closure glaucoma in the study eye, and this was considered related to aflibercept treatment by the study investigator. This TEAE was resolved, and the patient continued receiving aflibercept 8-mg treatment until the end of the trial with no repeated episodes of angle-closure glaucoma.

The incidence of intraocular inflammation events was low across all treatment groups (8q12, n = 6 [1.8%]; 8q16, n = 3 [0.9%]; 2q8, n = 7 [2.1%]; Table 3); all cases were mild or moderate in severity apart from 1 severe case of endophthalmitis in the 2q8 group. An additional event of endophthalmitis in the 2q8 group was considered mild, and both cases eventually resolved. No cases of occlusive retinal vasculitis were reported. Increased IOP events were reported in 12 patients (3.6%), 11 patients (3.3%) and 10 patients (3.0%) in the 8q12, 8q16, and 2q8 treatment groups, respectively. The proportion of patients with IOP of 35 mmHg or more at any time point (before or after injection) was comparable among the treatment groups (n = 3 [0.9%], n = 1 [0.3%], and n = 2 [0.6%] in the 8q12, 8q16, and 2q8 treatment groups, respectively; Table 3), with no indication of sustained IOP increases based on mean predose values during the trial (Fig S7, available at www.aaojournal.org).

The incidence of nonocular TEAEs and nonocular serious TEAEs was similar across the treatment groups through week 96, ranging from 73.1% to 76.5% and from 18.9% to 21.8%, respectively (Table 3). Thirty-three cases of adjudicated Anti-Platelet Trialists' Collaboration arterial thromboembolic events were reported with no clinically relevant differences observed across treatment groups (n = 5 [1.5%], n = 7 [2.1%], and n = 11 [3.3%] in the 8q12, 8q16, and 2q8 groups respectively). The incidence of hypertension TEAEs was similar across the treatment groups (ranging from 8.0% to 8.3%). Death was reported for 10 patients (3.0%), 7 patients (2.1%), and 12 patients (3.6%) patients in the 8q12, 8q16, and 2q8 groups, respectively (Table 3). None were considered related to aflibercept treatment.

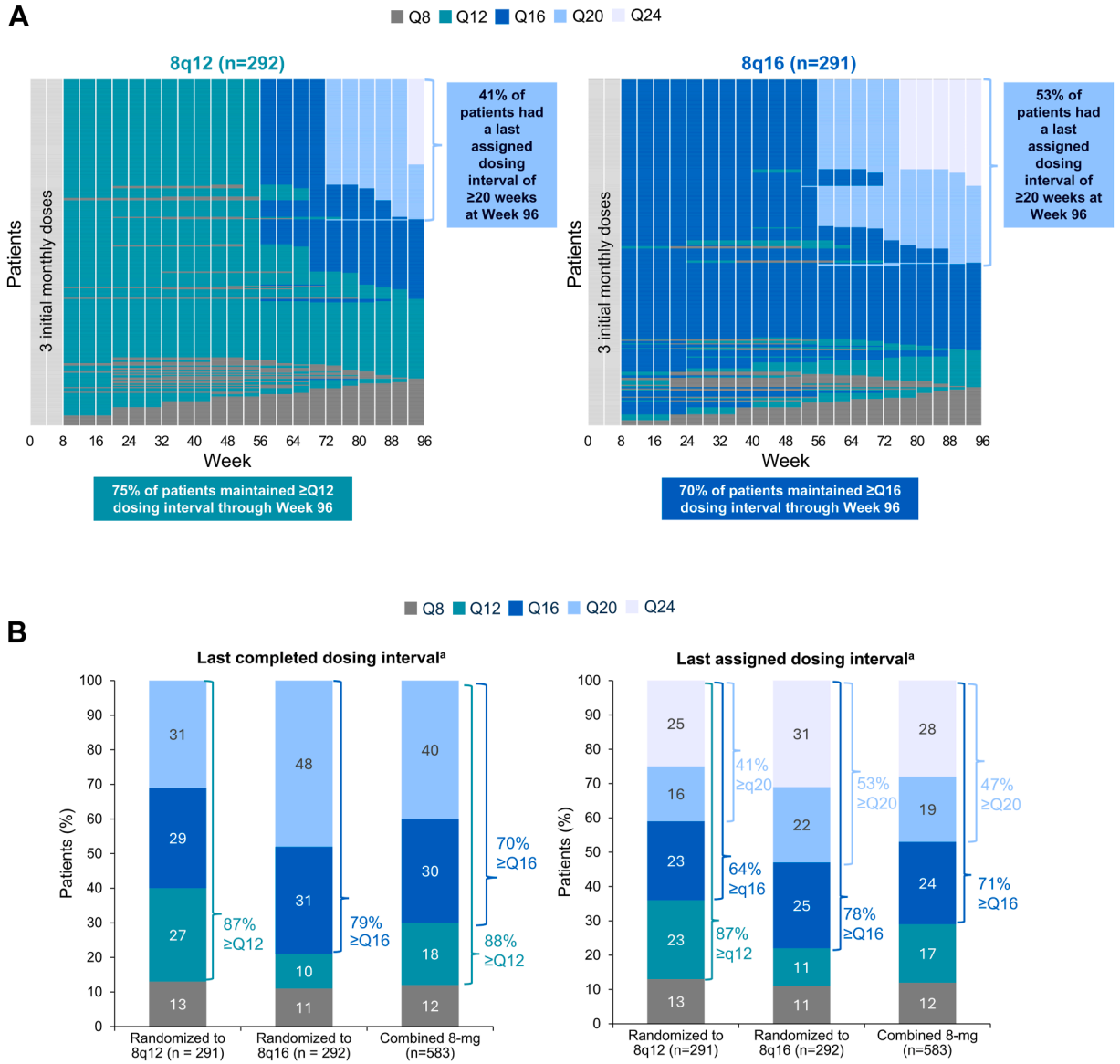


Figure 6. Graphs showing dosing intervals of aflibercept 8 mg-treated patients through week 96 (**A**) and last completed and last assigned dosing intervals in patients receiving aflibercept 8 mg through week 96 (**B**). **A,** Dosing intervals of each patient randomized to intravitreal aflibercept 8 mg every 12 weeks (8q12) (left) or intravitreal aflibercept 8 mg every 16 weeks (8q16) (right) are represented by a single horizontal line, or swim lane. **B,** Values may not add up to 100% because of rounding. Dosing intervals were shortened beginning at week 16 if patients showed a >5-letter loss in best-corrected visual acuity (BCVA) compared with week 12 because of persistent or worsening neovascular age-related macular degeneration and a >25-μm increase in central retinal thickness compared with week 12, or new foveal neovascularization, or new foveal hemorrhage. Dosing intervals were extended beginning at week 52 if patients had a <5-letter loss in BCVA compared with week 12 and no fluid at the center subfield on SD-OCT and no new foveal neovascularization or hemorrhage. [a]In patients completing week 96. 8q16 = aflibercept 8 mg every 16 weeks; 8q12 = aflibercept 8 mg every 12 weeks; Q8 = every 8 weeks; Q16 = every 16 weeks; Q12 = every 12 weeks; Q20 = every 20 weeks; Q24 = every 24 weeks.

Discussion

The efficacy and safety of aflibercept 8 mg with extended dosing intervals through week 48 in the PULSAR trial have been reported previously.[17] Consistent with results seen at week 48,[17] comparable BCVA gains were observed in the PULSAR trial at 96 weeks with aflibercept 8 mg (with extended dosing intervals) and 2 mg (every 8 weeks), with 8q12 and 8q16, remaining above the predefined noninferiority margin compared with 2q8. Anatomic improvements and fluid control achieved at week 48 with aflibercept 8 mg also were maintained through 96 weeks. Importantly, patients receiving aflibercept 8 mg were able to achieve and maintain visual and anatomic improvements comparable with those of patients receiving aflibercept 2 mg, with up to 5 fewer injections on average

Table 3. Treatment-Emergent Adverse Events Occurring through Week 96 (Safety Analysis Set)

Variable	Intravitreal Aflibercept Dosing Group			
	2 mg Every 8 Weeks (n = 336)	*8 mg Every 12 Weeks (n = 335)*	*8 mg Every 16 Weeks (n = 338)*	*Combined 8-mg (Every 12 Weeks and Every 16 Weeks; n = 673)*
Ocular TEAEs	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Serious	4 (1.2)	10 (3.0)	10 (3.0)	20 (3.0)
Treatment related	16 (4.8)	21 (6.3)	19 (5.6)	40 (5.9)
IOI events	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)
Iridocyclitis	1 (0.3)	0	3 (0.9)	3 (0.4)
Vitreal cells	2 (0.6)	1 (0.3	0	1 (0.1)
Endophthalmitis	2 (0.6)	0	0	0
Uveitis	1 (0.3)	1 (0.3)	0	1 (0.1)
Anterior chamber cell	0	1 (0.3)	0	0
Chorioretinitis	0	1 (0.3)	0	1 (0.1)
Eye inflammation	1 (0.3)	0	0	0
Hypopyon	1 (0.3)	0	0	0
Iritis	0	1 (0.3)	0	1 (0.1)
Vitritis	0	1 (0.3)	0	1 (0.1)
Patients with IOP ≥35 mmHg before or after injection	2 (0.6)	3 (0.9)	1 (0.3)	4 (0.6)
IOP or glaucoma-related TEAEs				
IOP increased	10 (3.0)	12 (3.6)	11 (3.3)	23 (3.4)
Ocular hypertension	1 (0.3)	4 (1.2)	4 (1.2)	8 (1.2)
Open-angle glaucoma	1 (0.3)	0	0	0
Angle-closure glaucoma	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)
Glaucoma	1 (0.3)	1 (0.3)	3 (0.9)	4 (0.6)
Nonocular TEAEs	257 (76.5)	253 (75.5)	247 (73.1)	500 (74.3)
Nonocular serious TEAEs	66 (19.6)	73 (21.8)	64 (18.9)	137 (20.4)
Treatment-emergent adjudicated APTC events	11 (3.3)	5 (1.5)	7 (2.1)	12 (1.8)
Cardiovascular death	5 (1.5)	3 (0.9)	2 (0.6)	5 (0.7)
Nonfatal myocardial infarction	4 (1.2)	1 (0.3)	4 (1.2)	5 (0.7)
Nonfatal stroke	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.3)
Treatment-emergent hypertension	27 (8.0)	27 (8.1)	28 (8.3)	55 (8.2)
Death	12 (3.6)	10 (3.0)	7 (2.1)	17 (2.5)

APTC = Anti-Platelet Trialists' Collaboration; 8q16 = intravitreal aflibercept 8 mg every 16 weeks; 8q12 = intravitreal aflibercept 8 mg every 12 weeks; IOI = intraocular inflammation; IOP = intraocular pressure; TEAE = treatment-emergent adverse event; 2q8 = intravitreal aflibercept 2 mg every 8 weeks.
Data are presented as no. (%).

(9.7 and 8.2 injections for 8q12 and 8q16 groups, respectively, vs. 12.8 injections for 2q8 group) over 96 weeks. On an individual basis, this could be up to 6 fewer injections for patients in the 8q16 group who were receiving aflibercept 8 mg every 20 weeks from week 56, thus receiving only 7 injections over 96 weeks. Notably, visual and anatomic outcomes in the second year (from weeks 48 to 96) were maintained with aflibercept 8 mg, with about half the number of injections on average (3.0 injections in the 8q16 group) compared with those administered in the 2q8 group (5.8 injections).

In the primary results of the PULSAR trial, 79% and 77% of patients assigned to the 8q12 and 8q16 groups, respectively, maintained 12-week and 16-week dosing intervals through week 48.[17] At week 96, 87% and 78% of patients randomized to the 8q12 and 8q16 groups achieved last assigned dosing intervals of 12 weeks or more and 16 weeks or more, respectively. Approximately 48% of patients in the 8q16 group completed a 20-week dosing interval, and 53% had a last assigned dosing interval of ≥20 weeks. In addition, 31% had a last assigned dosing interval of 24 weeks, indicating that dosing intervals of 24 weeks may be considered in aflibercept 8-mg treat-and-extend (T&E) regimens for patients with nAMD.

Visual and anatomic outcomes achieved in the first year were maintained through the second year of treatment, with dosing intervals extended beyond 16 weeks in most patients who received aflibercept 8 mg. Given that dosing interval extensions in the 8q12 and 8q16 groups were permitted only beginning from week 52 using stringent DRM criteria, it is notable that, by week 96, a high proportion of patients completed intervals longer than those originally randomized, with 31% and 48%, respectively, completing intervals of ≥ 20 weeks and 25% and 31%, respectively, being assigned even longer intervals of 24 weeks.

The DRM criteria for extension were consistent with clinical practice requiring stable visual acuity with no evidence of persistent or recurrent disease on OCT. Collectively, the efficacy and durability results from the PULSAR trial demonstrate that aflibercept 8 mg is able to provide

sustained disease control in nAMD as defined by the interrelated goals of maintaining vision gains, rapid and resilient fluid control without clinically meaningful fluctuation, and both with extended treatment intervals in a substantial proportion of patients.[21]

Previous studies of other intravitreal therapeutic agents with anti-VEGF mechanisms have examined the possibility of extended treatment intervals for nAMD. In the phase 3 HAWK and HARRIER trials (ClinicalTrials.gov identifiers, NCT02307682 and NCT02434328, respectively), brolucizumab 3 mg and 6 mg achieved comparable visual acuity outcomes versus 2q8 over 96 weeks, with a 40% to 45% probability of patients receiving brolucizumab 6 mg maintaining 12-week dosing intervals through the end of the second year.[6] In the phase 3 TENAYA and LUCERNE trials (ClinicalTrials.gov identifiers, NCT03823287 and NCT03823300, respectively), the efficacy and safety of the bispecific antibody faricimab 6 mg administered up to every 16 weeks was compared with that of 2q8.[5] Comparable vision gains were achieved with faricimab 6 mg and 2q8, with 45% and up to 66.9% of faricimab-treated patients achieving 16-week dosing intervals at weeks 48 and 112, respectively.[22] By comparison, the results of the PULSAR trial showed that dosing intervals with aflibercept 8 mg can be extended to up to 24 weeks, providing strong support for the potential of this treatment to reduce treatment burden.

We also reported on the comparable safety profile of aflibercept 8 mg with aflibercept 2 mg over 96 weeks, with similar incidence of ocular and nonocular TEAEs across all treatment groups. Through week 96, the proportions of patients with increased IOP or ocular hypertension were comparable across treatment groups. Intraocular pressure values before dosing in study eyes were similar in all arms and remained stable throughout the trial. The incidence of intraocular inflammation was low and comparable across treatment groups (ranging from 0.4% to 2.1%), with no cases of occlusive retinal vasculitis. All intraocular inflammation cases were mild or moderate in severity, except for 1 case of severe endophthalmitis in the 2q8 arm. No clinically relevant differences were observed in the proportions of patients experiencing hypertension events or Anti-Platelet Trialists' Collaboration events or in deaths across treatment groups.

A limitation of this trial was that the study design did not allow direct comparison of treatment effects between the aflibercept 8-mg and 2-mg groups at specific time points through week 96 because of the asynchronous dosing regimen after week 16. Further, trial conclusions were limited to treatment outcomes with dosing intervals of 20 weeks because this was the longest interval that could be completed within the 96-week study period. In addition, the study design limited comparisons of aflibercept 8 mg with aflibercept 2 mg dosed at a fixed interval, rather than with a T&E regimen. However, the availability of prior studies with aflibercept 2 mg using a T&E regimen allows for the comparison of durability outcomes between the 2 regimens. In the ALTAIR study (ClinicalTrials.gov identifier, NCT02305238) that evaluated 2 different aflibercept 2 mg T&E regimens (with 2- or 4-week adjustments), 57% and 60% of patients and 42% and 46% of patients achieved a final dosing interval of 12 weeks or more and 16 weeks, respectively, at week 96.[13] In the ARIES study (ClinicalTrials.gov identifier, NCT02581891) that assessed early-start vs late-start aflibercept 2 mg T&E regimens, dosing intervals were extended to $\geq$ 12 weeks and $\leq$ 16 weeks at week 104 in approximately 50% and 30% of patients, respectively, receiving aflibercept 2 mg.[14] In AZURE (ClinicalTrials.gov identifier, NCT02540954), 37% of patients receiving aflibercept 2 mg according to a T&E regimen after a year of fixed dosing achieved last dosing intervals of $\geq$ 12 weeks up to week 76.[23] These results suggest the existence of a maximum limit for the duration of treatment intervals with aflibercept 2 mg in most patients (up to 60% at dosing intervals of $\geq$ 12 or 16 weeks). In the PULSAR trial, the proportion of patients receiving aflibercept 8 mg with last completed dosing intervals of $\geq$ 12 weeks (88%) and $\geq$ 16 weeks (70%) at week 96 was markedly higher than that reported in the studies with an aflibercept 2-mg T&E regimen. Although we acknowledge that limitations are associated with cross-trial comparisons because of differences in study design, patient populations, and treatment durations, the results from the PULSAR trial suggest the ability of aflibercept 8 mg to extend dosing for longer intervals (with fewer injections) for more patients compared with aflibercept 2 mg with a T&E regimen. Additionally, it should be noted that findings with extended dosing intervals in the PULSAR trial are observed in a treatment-naive nAMD population. Patients who have responded suboptimally to prior treatments may require more frequent injections.

The strengths of this trial included the implementation of stringent DRM criteria wherein dosing intervals were extended at dosing visits only in patients receiving aflibercept 8 mg who lost fewer than 5 letters in BCVA from week 12, with no fluid in the center subfield on SD-OCT and no new foveal hemorrhage or foveal neovascularization. Despite these stringent criteria, almost 50% of patients across both aflibercept 8-mg groups achieved dosing intervals of $\geq$ 20 weeks through week 96. Furthermore, 86% of patients completed treatment through week 96, allowing for a robust analysis of the long-term efficacy and safety profile of aflibercept 8 mg in a sizeable population. The long-term efficacy, safety, and durability of aflibercept 8 mg has been assessed further in the optional open-label extension phase of the PULSAR trial (PULSAR Extension) through 156 weeks, which evaluated outcomes in patients who continued to receive aflibercept 8 mg at extended intervals and in those who were switched from aflibercept 2q8 to aflibercept 8 mg.

In summary, we showed that aflibercept 8 mg administered at extended dosing intervals of up to 20 weeks resulted in similar visual gains and comparable anatomic improvements as 2q8, with no new safety concerns, over 96 weeks. These results were achieved with up to 5 fewer injections in the 8q16 group compared with the 2q8 group. Dosing intervals were maintained or extended in most patients receiving aflibercept 8 mg, with up to 48% in the

8q16 group having a last completed dosing interval of 20 weeks at week 96. The less frequent dosing required with aflibercept 8 mg compared with other agents may result in decreased treatment burden, potentially leading to increased patient adherence and improved treatment outcomes. The results of this study demonstrating the long-term efficacy and safety of aflibercept 8 mg at extended dosing intervals support aflibercept 8 mg as a treatment option for achieving sustained disease control in patients with nAMD.

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Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing." This pertains to scope, time point and process of data access. As such, Bayer commits to sharing, on request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States and European Union as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the European Union and United States regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

HUMAN SUBJECTS: Human subjects were included in this study. The trial was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, and applicable local laws and regulations. The protocol was reviewed and approved by the relevant institutional review boards and independent ethics committees (as listed in the Appendix available at www.aaojournal.org) before the trial was initiated. All patients provided written informed consent before participating in the trial.

No animal subjects were included in this study.

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Abbreviations and Acronyms:
AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CRT** = central retinal thickness; **DRM** = dose regimen modification; **8q16** = intravitreal aflibercept 8 mg every 16 weeks; **8q12** = intravitreal aflibercept 8 mg every 12 weeks; **FAS** = full analysis set; **ICE** = intercurrent event; **IOP** = intraocular pressure; **LS** = least squares; **MMRM** = mixed model for repeated measures; **nAMD** = neovascular age-related macular degeneration; **SAE** = serious adverse event; **SD** = spectral-domain; **T&E** = treat-and-extend; **TEAE** = treatment-emergent adverse event; **2q8** = intravitreal aflibercept 2 mg every 8 weeks.

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