Effect of Key Baseline Disease Characteristics on Aflibercept 8 mg Dosing Interval Extension

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A Post Hoc 96-Week Analysis of PULSAR

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Objective: Post hoc analysis of the PULSAR phase 3 trial (NCT04423718) to determine whether dosing interval outcomes were associated with key baseline disease characteristics.

Design: Exploratory post hoc analysis of PULSAR, a 96-week, double-masked, active-controlled, randomized clinical trial in patients with treatment-naïve neovascular age-related macular degeneration (nAMD) treated with aflibercept 8 mg or aflibercept 2 mg. For the main analysis, patients receiving aflibercept 8 mg were grouped according to their last assigned dosing interval at weeks 48 and 96.

Participants: Patients with treatment-naïve nAMD who were randomly assigned to receive aflibercept 8 mg in PULSAR.

Intervention: Aflibercept 8 mg was administered every 12 weeks (8q12) or 16 weeks (8q16), each after 3 initial monthly injections. Dosing intervals could be shortened in year 1 based on prespecified disease activity criteria, whereas in year 2, both interval shortening and extension were allowed. Patients were monitored every 4 weeks but assessed for interval modification at dosing visits only.

Main Outcome Measures: Baseline best-corrected visual acuity (BCVA), central retinal thickness (CRT), and macular neovascularization (MNV) area were assessed in patients grouped by their last assigned dosing interval (Q8, Q12, Q16, Q20, or Q24) at weeks 48 and 96.

Results: In 86.6% and 78.4% of patients assigned to the 8q12 and 8q16 arms in PULSAR, respectively, randomized dosing intervals were maintained or extended through week 96. In the 8q12 arm, no trends were observed in baseline BCVA, CRT, and MNV area across groups based on patients' last assigned dosing intervals. In the 8q16 arm, no trends were observed in baseline BCVA across treatment arms; however, patients with shorter last assigned dosing intervals (Q8 and Q12) at weeks 48 and 96 tended to have a greater baseline CRT or MNV area compared with patients with longer dosing intervals (Q16–Q24).

Conclusions: Overall, findings from this PULSAR post hoc analysis of key baseline characteristics in patients grouped by dosing interval suggest that the aflibercept 8q12 and 8q16 regimens were suitable for most patients across a broad range of baseline BCVA, CRT, and MNV area values, with a large proportion of patients able to achieve and maintain extended dosing intervals through week 96.

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Age-related macular degeneration (AMD) affects more than 200 million people worldwide[1,2] and is a leading cause of blindness.[1,3] Neovascular AMD (nAMD) comprises only approximately 15% of AMD cases but is associated with the most severe vision loss.[4] Given the severity of nAMD, this disease imposes a substantial burden on patients, caregivers, and health care systems, with patients facing multiple barriers to treatment.[5]

Major advances in nAMD treatment have been made possible with the advent of anti-VEGF therapies.[6,7] Various anti-VEGF treatment regimens have been evaluated in clinical trials, including fixed monthly or bimonthly

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injections, as-needed dosing, and treat-and-extend regimens.[8] Clinicians now predominantly use the treat-and-extend regimen in clinical practice, with dosing intervals modified based on disease activity markers.[6,8]

Data from clinical trials and observational studies suggest that ~1 in 4 patients with nAMD continue to need frequent anti-VEGF treatment long-term, requiring injections every ≤6 weeks.[6,9] There remains a lack of consensus regarding the best treatment algorithm for nAMD, including what constitutes a good treatment response and which criteria to use when deciding to extend or shorten dosing intervals.[10–12] Thus, unmet needs remain for a standardized, evidence-based treatment protocol and durable therapies to help reduce treatment burden.[5,6,9,13] Advancements in these areas could potentially improve treatment adherence, persistence, and long-term visual outcomes in patients.[6,14]

Several demographic, genetic, lifestyle, and disease factors have been widely reported in the literature to predict clinical outcomes in nAMD.[6,11,15,16] In contrast, much less research has focused on baseline characteristics that may correlate with the likelihood of dosing interval shortening or extension in flexible treatment regimens; most studies only indirectly touch on this aspect by assessing injection frequency.[11,15] However, patients generally considered likely to have poor clinical outcomes tend to be older, have a lower best-corrected visual acuity (BCVA), greater central retinal thickness (CRT), and larger macular neovascularization (MNV) area at baseline,[15–22] and may, therefore, require more frequent anti-VEGF injections to optimize outcomes.

Aflibercept 8 mg received regulatory approval for the treatment of nAMD[23,24] based on findings from the PULSAR trial.[25] PULSAR (NCT04423718) was a 96-week, randomized, double-masked, and active-controlled phase 3 trial conducted across 27 countries in treatment-naïve adults with nAMD.[25,26] The PULSAR trial evaluated the efficacy and safety of aflibercept 8 mg every 12 weeks (8q12) or 16 weeks (8q16) versus aflibercept 2 mg every 8 weeks (2q8), each after 3 initial monthly injections. In the aflibercept 8 mg arms, the dosing interval could be shortened in year 1 based on prespecified disease activity criteria, whereas in year 2, both dosing interval shortening and extension were allowed. Both aflibercept 8 mg groups achieved the primary end point of noninferior improvement in BCVA compared with aflibercept 2q8 at week 48 (noninferiority margin, 4 letters), with most patients maintaining their randomly assigned dosing intervals (8q12, 79%; 8q16, 77%). The visual and anatomic improvements observed through week 48 in patients treated with aflibercept 8 mg were maintained through week 96 over extended dosing intervals, with outcomes comparable to those treated with aflibercept 2 mg on a fixed regimen of every 8 weeks. At week 96, 87% of patients in the 8q12 group and 78% in the 8q16 group were on last assigned dosing intervals of ≥12 and ≥16 weeks, respectively. Through week 96, the safety profiles of aflibercept 8 and 2 mg were also comparable, with no safety concerns identified. These findings suggest that with aflibercept 8 mg, dosing intervals of most patients may be extended to Q12 or Q16 after 3 initial monthly doses and maintained over time, without compromising safety.[25,26]

Although PULSAR demonstrated the efficacy and safety of aflibercept 8 mg with extended dosing intervals for the treatment of nAMD, it remains unclear whether baseline functional or anatomic parameters are associated with the sustainability of dosing intervals. The objective of this exploratory PULSAR post hoc subgroup analysis was to descriptively assess whether key baseline disease characteristics—BCVA, CRT, and MNV area—may be associated with patients' dosing intervals through weeks 48 and 96.

Methods

Study Design

The present study is a post hoc analysis of the PULSAR trial (available at http://www.clinicaltrials.gov: NCT04423718), the study design and results of which have been described previously.[25,26] In brief, PULSAR was a randomized, double-masked, active-controlled, noninferiority, phase 3 trial that compared the efficacy and safety of aflibercept 8 mg with that of aflibercept 2 mg over 96 weeks in treatment-naïve patients aged ≥50 years with nAMD. The primary end point was the change in BCVA from baseline to week 48. Eligible patients were randomly assigned 1:1:1 to either aflibercept 8 mg every 12 weeks (8q12), aflibercept 8 mg every 16 weeks (8q16), or aflibercept 2 mg every 8 weeks (2q8), each after 3 initial monthly injections. One eye per patient was designated as the study eye. Patients, study investigators, and the central reading center were masked to the treatment arms, with sham injections administered at visits not scheduled for an active injection.

In PULSAR, patients in the aflibercept 2 mg arm remained on a fixed dosing regimen, whereas those in the aflibercept 8 mg arms could have their dosing interval shortened from week 16 through 96 or extended from week 52 through 96, provided that the prespecified dose regimen modification criteria were met.[26] Dose regimen modification criteria for interval shortening were a BCVA loss of >5 letters from week 12 and either a >25-μm increase in CRT from week 12 or new foveal hemorrhage or neovascularization. Patients in the aflibercept 8 mg arms who met these criteria at weeks 16 or 20 had their dosing interval shortened to every 8 weeks (Q8). Those who met the criteria after week 24 had their dosing interval shortened by 4 weeks. The minimum dosing interval was Q8, and dosing intervals could not be extended within the first year of the trial.

From week 52 to 96, patients in the aflibercept 8 mg groups could have their dosing interval extended by 4-week increments if the dose regimen modification criteria for interval extension were met. Dose regimen modification criteria for interval extension were a <5-letter loss in BCVA compared with week 12, no fluid in the center subfield (per spectral-domain OCT), and no new-onset foveal hemorrhage or foveal neovascularization.[26] The maximum dosing interval permitted in year 2 of the study was every 24 weeks (Q24). Dosing interval extension was only permitted at active injection visits.

The trial was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice Guidelines, and all applicable local laws and regulations in each country. The protocol was reviewed and approved by the relevant institutional review boards and independent ethics committees at each study site before the trial was initiated. All patients provided written informed consent before participating in the trial.

Baseline Characteristics

Baseline BCVA was assessed using ETDRS letter scores. The average retinal thickness within the center subfield (CRT) was measured with spectral-domain OCT, in which the center subfield was defined as a circle with a diameter of 1 mm centered on the fovea. All BCVA and CRT assessments were conducted under masked conditions with respect to the patients' assigned treatment arms.

Macular neovascularization area was assessed with fundus photography/fluorescein angiography at prespecified visits throughout the study (at screening and weeks 12, 24, 36, 48, 60, and 96). The same imaging system used at screening was used at all subsequent visits for each patient, and images were taken before dosing (active or sham injections). Images were evaluated by masked certified readers at a central reading center. Macular neovascularization area was measured by planimetry during the early-to-mid phases of the fundus photography/fluorescein angiography using Macular Photocoagulation Study-based grading criteria.[27] Reading center quality assurance procedures included longitudinal review of serial images and monitoring of intergrader agreement.

The cutoffs applied in the analysis of the last assigned dosing intervals in patients grouped by baseline characteristics were as follows: (1) BCVA: ≤54, 55 to 73, and ≥74 letters; (2) CRT: <279, 279 to <344, 344 to <423, and ≥423 μm; and (3) MNV area: <1.3, 1.3 to <5.0, and ≥5.0 mm^2. The BCVA cutoffs correspond to clinically recognizable Snellen-equivalent visual acuity categories based on standard ETDRS letter score conversions: ≤54 letters (~≤20/80 Snellen) represents poorer baseline vision, 55 to 73 letters (~20/80–20/40 Snellen) represents moderate impairment, and ≥74 letters (~≥20/32 Snellen) represents good baseline vision. The CRT cutoffs applied in this analysis are quartile-based to ensure balanced group sizes (~250 patients per CRT category). The MNV area cutoffs were selected to reflect clinically meaningful size groupings, with <1.3 mm^2 representing small, focal lesions, 1.3 to <5 mm^2 reflecting intermediate-sized lesions, and ≥5 mm^2 reflecting larger, more extensive lesions.

Post Hoc Analysis

For the first part of this post hoc subgroup analysis, patients in the aflibercept 8 mg treatment arms (8q12 and 8q16) who completed the week 48 or 96 visit were grouped according to their last assigned dosing interval at these timepoints (8 weeks [Q8], 12 weeks [Q12], 16 weeks [Q16], 20 weeks [Q20], or 24 weeks [Q24]). Key baseline characteristics (mean BCVA, CRT, and MNV area) of patients in each subgroup were described to explore whether any of these characteristics were associated with trends in the patients' last assigned dosing intervals at weeks 48 and 96. In the second part of this analysis, patients in the aflibercept 8q12 and 8q16 arms who completed the week 96 visit were grouped by their baseline characteristics (i.e., subgroups defined by mean baseline BCVA, CRT, and MNV area) to explore trends in the last assigned dosing intervals at week 96 between subgroups. Only the aflibercept 8 mg arms were included in the above analyses, given that dosing interval modifications were not permitted in the 2q8 arm.

In a final analysis, patients who completed the week 48 and 96 visits were grouped according to their effective dosing interval through weeks 48 and 96 to investigate whether there were any trends in baseline characteristics (BCVA, CRT, and MNV area) across these groups (further details are provided in the associated Supplemental Methods S1, available at https://www.ophthalmologyretina.org).

Statistical Analysis

This was an exploratory analysis, and no hypotheses were tested. All analyses were based on the safety analysis set (all patients who received ≥1 dose of the study drug). Data were analyzed descriptively with frequency distributions, percentages, and summary statistics. Statistical analyses were performed using the Statistical Analysis System software, version 9.4 or higher (SAS Institute Inc).

Results

Patients

The baseline demographics and disease characteristics of patients in the 8q12 and 8q16 arms in PULSAR have been previously reported and were generally comparable,[25] as were the characteristics of patients in the overall full analysis set versus those who completed the week 96 visit (data on file). In PULSAR, the mean age of patients receiving aflibercept 8 mg was 74.6 years, and 53.8% were female; patients had a mean ± standard deviation (SD) baseline BCVA of 59.9 ± 12.9 letters, CRT of 371 ± 128 μm, and MNV area of 6.3 ± 5.2 mm^2.[25]

Last Assigned Dosing Intervals at Weeks 48 and 96

Of the 673 patients who were randomly assigned to aflibercept 8 mg treatment, 628 (93.3%) and 583 (86.6%) completed weeks 48 and 96, respectively. At week 48, 79.4% of patients in the 8q12 arm and 76.6% in the 8q16 arm who completed week 48 had a last assigned dosing interval of 12 and 16 weeks, respectively (Fig 1A). Among patients who completed week 96, 86.6% of patients in the 8q12 arm and 78.4% in the 8q16 arm had a last assigned interval of ≥Q12 and ≥Q16 weeks at week 96, respectively, and 46.8% and 27.8% of patients receiving aflibercept 8 mg (8q12 and 8q16) had a last assigned dosing interval of ≥Q20 and Q24, respectively (Fig 1B).

Baseline Characteristics in Patients Grouped by Last Assigned Dosing Interval at Weeks 48 and 96

Best-Corrected Visual Acuity. In patients receiving aflibercept 8 mg who were grouped by their last assigned dosing interval at week 48, no trends were observed in mean baseline BCVA (range, 56.4–61.7 letters across the 8q12 and 8q16 arms; Fig 2A). Similarly, the mean baseline BCVA showed minimal variation between subgroups at week 96 (range, 57.9–62.4 letters across the 8q12 and 8q16 arms). Summary statistics for these data are provided in Table S1 (available at https://www.ophthalmologyretina.org).

Central Retinal Thickness. The mean baseline CRT was similar among patients in the aflibercept 8q12 arm when grouped by the last assigned dosing interval at week 48 (range, 367–372 μm) and week 96 (range, 351–393 μm; Fig 2B and Table S1). In the aflibercept 8q16 arm, the mean baseline CRT was numerically greater among patients on the last assigned dosing intervals of Q8 and Q12 at both week 48 (range, 427–445 μm) and week 96 (range, 417–452 μm) compared with those on the last assigned dosing interval of Q16 at week 48 (353 μm) and ≥Q16 at week

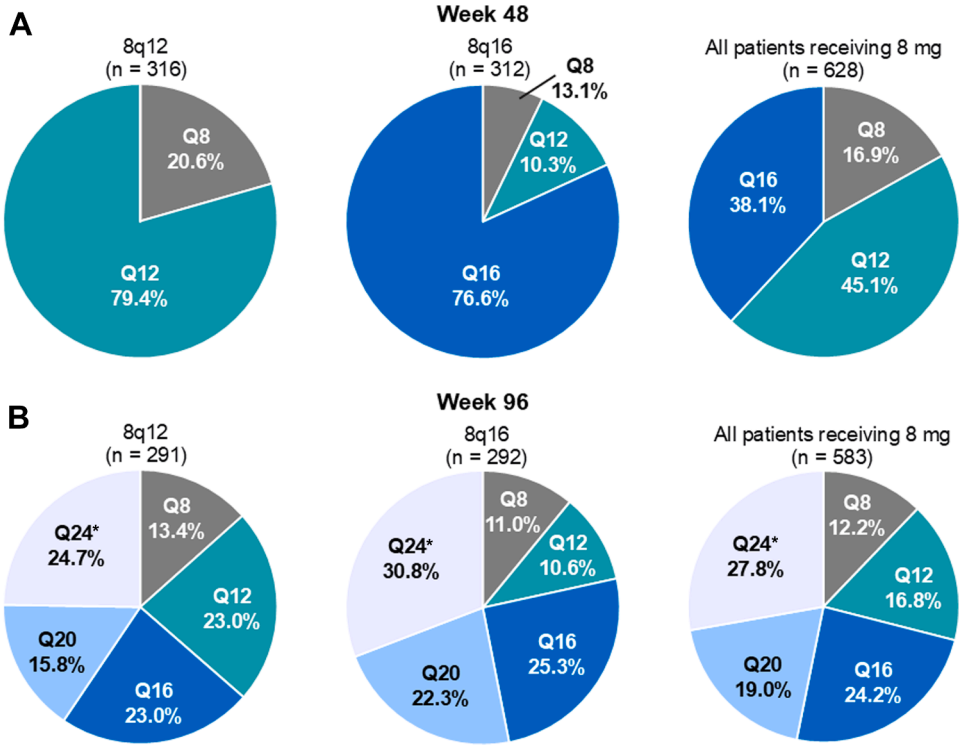

Figure 1. Last assigned dosing intervals at week 48 (**A**) and week 96 (**B**). Data are for patients in the safety analysis set who completed the week 48 (A) and week 96 (B) visits. *Patients assigned to a 24-week dosing interval only had sufficient time to complete 20 weeks by Week 96. 8q12 = aflibercept 8 mg every 12 weeks after 3 initial monthly injections; 8q16 = aflibercept 8 mg every 16 weeks after 3 initial monthly injections; Q8 = dosing every 8 weeks; Q12 = dosing every 12 weeks; Q16 = dosing every 16 weeks; Q20 = dosing every 20 weeks; Q24 = dosing every 24 weeks.

96 (range, 353−364 μm). Thus, a trend was noted in the 8q16 arm, although the differences between dosing interval groups were small relative to the SDs.

Macular Neovascularization Area. The mean baseline MNV area was quite variable among subgroups, with large SDs observed (Fig 2C and Table S1). Among patients in the 8q12 arm grouped by their last assigned dosing interval at weeks 48 and 96, the mean baseline MNV area ranged from 5.9 to 6.0 mm^2 and from 5.1 to 7.3 mm^2, respectively. In the 8q16 arm, the mean baseline MNV area was numerically larger among patients assigned to shorter (Q8 and Q12) versus longer (≥Q16) dosing intervals at both week 48 (range, 6.4−7.5 mm^2) and week 96 (range, 6.1−8.3 mm^2). Thus, a potential trend was again noted in the 8q16 arm, although the differences between dosing interval groups were small compared with the SDs.

Last Assigned Dosing Intervals at Week 96 in Patients Grouped by Baseline Characteristics

Best-Corrected Visual Acuity. At week 96, no trends were observed in the distribution of the last assigned dosing intervals among aflibercept 8 mg-treated patients grouped by baseline BCVA (≤54, 55−73, and ≥74 letters; Fig 3A).

Central Retinal Thickness. Among patients in the 8q12 arm, no trends were observed in the distribution of last assigned dosing intervals at week 96 in patients grouped by baseline CRT (<279, 279−<344, 344−<423, and ≥423 μm; Fig 3B). In the 8q16 arm, the combined proportion of patients on a last assigned dosing interval of Q8 or Q12 increased from 9% to 33% across the baseline CRT categories of <279 to ≥423 μm.

Macular Neovascularization Area. At week 96, no trends were observed in either treatment arm in the distribution of the last assigned dosing intervals among patients grouped by baseline MNV area (<1.3, 1.3 to <5, and ≥5 mm^2; Fig 3C).

Baseline Characteristics in Patients Grouped by the Effective Dosing Interval through Weeks 48 and 96

Baseline characteristics (BCVA, CRT, and MNV area) were further evaluated in patients grouped according to their effective dosing interval through weeks 48 and 96: patients whose dosing intervals were shortened to every 8 weeks, maintained at every 12 or 16 weeks, or maintained as per their randomized schedule and then extended to every 20 or 24 weeks without interval shortening (see Fig S1, Table S2, and further details in the associated Methods S1, available at https://www.ophthalmologyretina.org).

Similar to the analysis described above, no trends in baseline BCVA were observed through weeks 48 and 96 within the 8q12 and 8q16 arms across these dosing interval groups, whereas baseline CRT and MNV area tended to be lower in groups with longer dosing intervals in the 8q16 arm but not in the 8q12 arm. It should be noted that the observed differences between dosing interval groups were small compared with the SDs, particularly for MNV area.

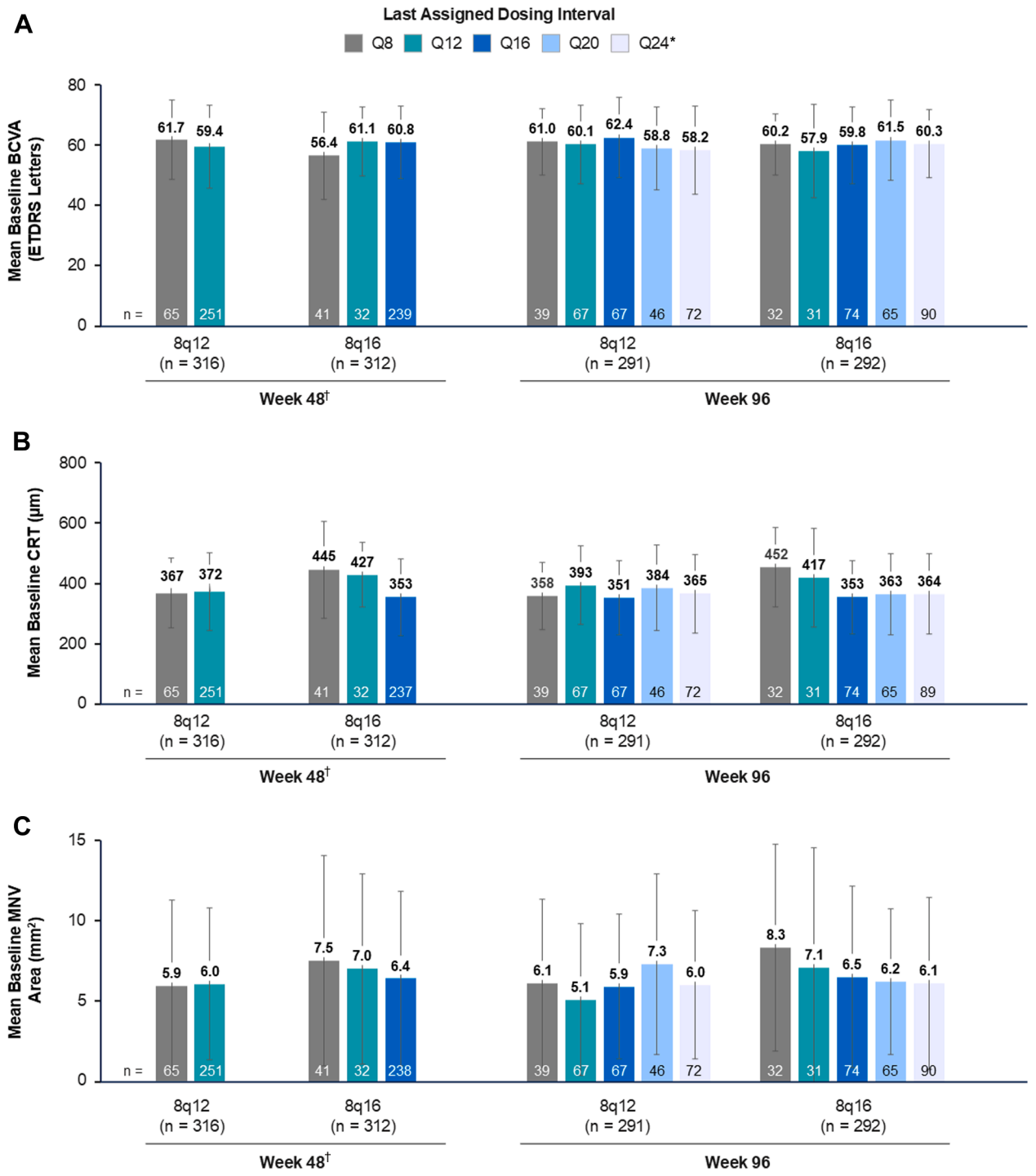

Figure 2. Baseline BCVA (**A**), CRT (**B**), and MNV area (**C**) of patients grouped by their last assigned dosing interval among those who completed the week 48 or 96 visit. Data shown represent mean (error bars, standard deviation) for patients in the safety analysis set who completed the week 48 or 96 visit. *Patients assigned to a 24-week dosing interval only had sufficient time to complete 20 weeks by week 96. †Patients could shorten but not extend dosing intervals in year 1; therefore, 48-week completers had a last assigned dosing interval of either that which they had been randomly assigned to or shorter. 8q12 = aflibercept 8 mg every 12 weeks after 3 initial monthly injections; 8q16 = aflibercept 8 mg every 16 weeks after 3 initial monthly injections; BCVA = best-corrected visual acuity; CRT = central retinal thickness; MNV = macular neovascularization; Q8 = dosing every 8 weeks; Q12 = dosing every 12 weeks; Q16 = dosing every 16 weeks; Q20 = dosing every 20 weeks; Q24 = dosing every 24 weeks.

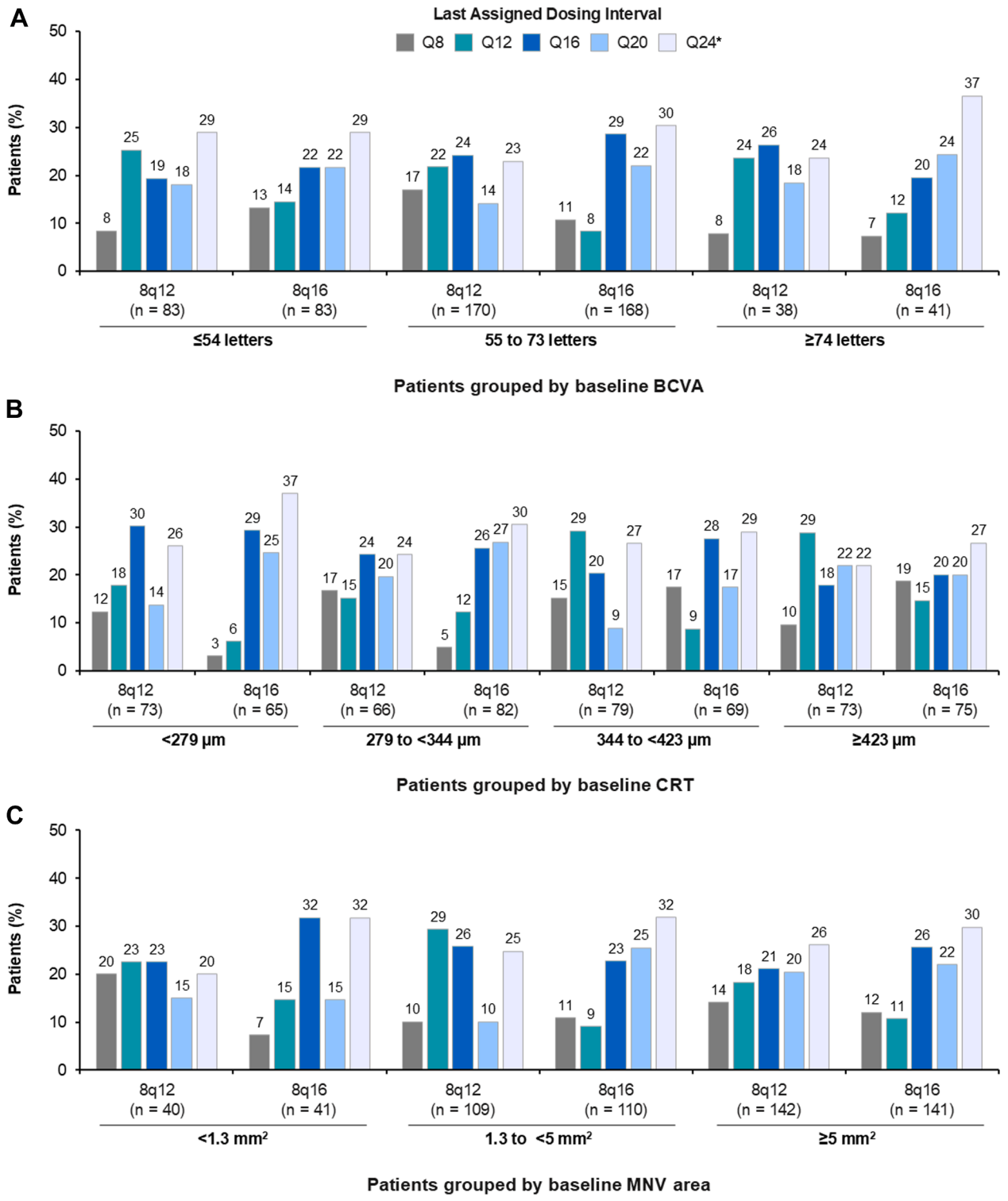

Figure 3. Proportion of patients at each last assigned dosing interval among those who completed the week 96 visit and were grouped by the baseline characteristics BCVA (**A**), CRT (**B**), and MNV area (**C**). Data shown are for patients in the safety analysis set who completed the week 96 visit. *Patients assigned to a 24-week dosing interval only had sufficient time to complete 20 weeks by week 96. 8q12 = aflibercept 8 mg every 12 weeks after 3 initial monthly injections; 8q16 = aflibercept 8 mg every 16 weeks after 3 initial monthly injections; BCVA = best-corrected visual acuity; CRT = central retinal thickness; MNV = macular neovascularization; Q8 = dosing every 8 weeks; Q12 = dosing every 12 weeks; Q16 = dosing every 16 weeks; Q20 = dosing every 20 weeks; Q24 = dosing every 24 weeks.

Discussion

In the PULSAR trial, patients with treatment-naïve nAMD who were randomly assigned to receive aflibercept 8 mg were extended to dosing intervals of either 12 weeks (8q12) or 16 weeks (8q16) immediately after 3 initial monthly doses.[25] Dosing intervals could subsequently be modified based on predefined functional and anatomic criteria. Although study visits occurred every 4 weeks, patients were assessed for eligibility for interval modifications multiple times throughout the trial at dosing visits only, similar to routine clinical practice. Patients' dosing interval journeys throughout the study are illustrated in detail in the primary publications of the PULSAR week 48 and 96 findings.[25,26]

To help inform the management of patients with nAMD, a post hoc subgroup analysis of PULSAR was conducted to descriptively assess trends between patients' last assigned dosing intervals and baseline BCVA, CRT, and MNV area with aflibercept 8 mg. In this analysis, patients receiving aflibercept 8 mg were grouped based on their last assigned dosing interval at weeks 48 and 96 (Q8, Q12, Q16, Q20, or Q24). Three key baseline disease characteristics that may be associated with clinical outcomes were assessed across these groups.[15,19,20] The analyses suggested that these baseline characteristics (BCVA, CRT, and MNV area) were not linked to dosing interval shortening or extension when patients were treated with aflibercept 8q12 after 3 initial monthly doses. In the aflibercept 8q16 arm, no trends were observed in baseline BCVA based on the last assigned dosing interval, whereas patients with shorter last assigned dosing intervals (Q8 and Q12) at weeks 48 and 96 showed a modest trend toward greater baseline CRT compared with patients with longer dosing intervals (Q16−Q24). Similar results were observed for MNV area, where patients with shorter last assigned dosing intervals showed a trend toward larger baseline MNV area compared with patients with longer dosing intervals, albeit with small differences in MNV area between groups. These findings align with the authors' clinical experience that a greater CRT and larger MNV area at baseline are indicative of more advanced and chronic disease.

In a further analysis, dosing interval outcomes at week 96 were evaluated in patients grouped by their baseline BCVA, CRT, and MNV area. No trends were observed in dosing interval outcomes among patients grouped by baseline BCVA or MNV area in either of the aflibercept 8q12 or 8q16 treatment arms. In patients grouped by baseline CRT, the aflibercept 8q16 arm showed a trend toward higher proportions of patients with last assigned dosing intervals of Q8 and Q12 as baseline CRT increased.

The differences in the trends observed in the above analyses between the 8q12 and 8q16 groups might, to some extent, be explained by the fact that patients in the 8q12 group required two 4-week extension steps to reach Q20 or longer intervals. Directly extending dosing to Q16 after the initial dosing phase may require subsequent dosing interval shortening in some patients, particularly in those with a greater baseline CRT or MNV area.

Overall, the results of the PULSAR trial,[25,26] this post hoc analysis, and a recent meta-analysis[28] suggest that the aflibercept 8q12 and 8q16 regimens are suitable for most patients with nAMD; even patients with advanced disease at baseline can potentially achieve extended dosing intervals of 20 weeks or longer. However, patients with a greater CRT or MNV area at baseline will need careful monitoring. Clinicians may need to exercise caution in assigning these patients to Q16 dosing intervals directly after initial monthly dosing.

Although some studies have not observed an association between baseline CRT and treatment response,[15,17] others have indicated that a greater CRT at baseline may predict suboptimal visual acuity outcomes. Increased MNV area at baseline is also generally considered to be predictive of suboptimal outcomes.[15,16,19,20] The present findings that a greater CRT and MNV area at baseline may be associated with higher treatment burden are, therefore, consistent with these analyses.

This post hoc analysis was based on clinical trial data in which patients' dosing intervals were closely managed and modified according to specific predefined dose regimen modification criteria, which enabled the analysis of trends based on dosing interval subgroups. It must be acknowledged that these criteria included changes in BCVA and CRT, which were also among the baseline characteristics assessed in the present analysis; therefore, the dosing interval outcomes evaluated here were not independent of these baseline characteristics. Furthermore, given the limited sample sizes of many of the subgroups, as well as the exploratory, post hoc nature of this study, all analyses were descriptive only, and the aim of the study was not to predict dosing interval durability based on baseline characteristics (i.e., no predictive models were formulated). The generalizability of the present findings must be considered in light of the inherent limitations discussed earlier, and dedicated prospective studies are required to confirm the observed trends. A further limitation of this analysis is that additional baseline disease characteristics previously linked to treatment outcomes were not investigated, such as intraretinal and subretinal fluid, pigment epithelial detachment, subretinal hyperreflective material, hyperreflective foci, and nAMD lesion subtype,[11,16,22] which may be more closely associated with treatment demand and the ability to sustain extended dosing intervals.

Unlike AMD in general, nAMD does not seem to differ in prevalence between male and female patients or among different racial groups,[1] although male sex may be associated with poorer prognoses,[15,21] Black patients may have better visual outcomes, and the prevalence of nAMD subtypes may differ between racial groups.[21] The present analysis did not examine the effect of race or sex. Furthermore, only treatment-naïve patients fulfilling specific inclusion and exclusion criteria were included in the PULSAR study. These factors also affect the generalizability of the findings of the present analysis.

In the PULSAR trial, patients' dosing intervals with aflibercept 8 mg were extended to Q12 and Q16 after 3 initial monthly doses. However, it is not yet known whether these extended dosing intervals are suitable for all patients after initial monthly dosing, and the criteria used to modify dosing intervals in the PULSAR trial may differ from those employed in clinical treatment settings.[11] Thus, observational studies are needed to evaluate outcomes with aflibercept 8 mg in routine clinical practice. Finally, the first 2 analyses described in this post hoc analysis assessed dosing intervals at specific endpoints (weeks 48 and 96), which may have obscured clinically meaningful changes in patients' dosing intervals through the course of the study.

In conclusion, the findings of this post hoc analysis of PULSAR suggest that the high-dose aflibercept 8q12 and 8q16 regimens after initial monthly dosing may benefit most patients with nAMD, including many with more severe baseline disease; however, for certain patients with higher anatomic burden at baseline, closer monitoring may be needed along with a more cautious approach to early extension. In PULSAR, patients who completed week 96 in the 8q12 and 8q16 arms received a mean total of 9.7 and 8.2 injections from baseline, respectively. Most patients in these treatment arms responded well to treatment and did not require subsequent interval shortening;[26] furthermore, their safety outcomes were comparable to those of patients administered with aflibercept 2 mg every 8 weeks.[25] Overall, these data are consistent with early analyses regarding aflibercept 8 mg treatment durability,[28–31] with most patients being able to extend to Q12 or Q16 after initial monthly dosing and further extensions subsequently possible depending on treatment response. Given the exploratory nature of this post hoc analysis, further confirmatory analyses are required to fully elucidate any potential associations between key baseline characteristics and dosing intervals with aflibercept 8 mg.

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Footnotes and Disclosures

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Data Availability: Availability of the data underlying this publication will be determined later according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America "Principles for responsible clinical trial data sharing." This pertains to the scope, time point, and process of data access. As such, Bayer commits to sharing upon 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 EU and US 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 to 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.

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No animal subjects were used in this study.

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Data collection: Garweg, Chaudhary, Zhang, Leal, Machewitz, Munk, Zarranz-Ventura, Stahl, Lanzetta

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Abbreviations and Acronyms:
2q8 = aflibercept 2 mg every 8 weeks after 3 initial monthly injections; **8q12** = aflibercept 8 mg every 12 weeks after 3 initial monthly injections; **8q16** = aflibercept 8 mg every 16 weeks after 3 initial monthly injections; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CRT** = central retinal thickness; **MNV** = macular neovascularization; **nAMD** = neovascular age-related macular degeneration; **Q(n)** = administered every n weeks; **SD** = standard deviation.

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