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## COMMENT OPEN



# Sustained disease control with aflibercept 8 mg: a new benchmark in the management of retinal neovascular diseases

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Retinal neovascular diseases, such as neovascular age-related macular degeneration (nAMD), diabetic retinopathy (DR), diabetic macular oedema (DMO), and retinal vein occlusion (RVO), are major causes of visual impairment worldwide [1–3]. Vascular endothelial growth factor (VEGF) is considered critical in the pathophysiology of these conditions and randomized trials have established the efficacy and safety of agents with an anti-VEGF mechanism of action [4]. Extensive real-world studies of ranibizumab or aflibercept 2 mg have also demonstrated that effectiveness in clinical practice is possible [5–8], including maintenance of vision gains through 4 years with a proactive treat-and-extend (T&E) regimen in patients with nAMD [5], and vision gains over 3 years with a meaningful reduction in treatment burden after early, consistent dosing in patients with DMO [6].

Patients, physicians, and caregivers generally prefer regimens with fewer clinic visits, and although T&E regimens allow gradual treatment interval extensions once disease inactivity is verified, treatment burden to achieve optimal outcomes can remain high [9, 10]. Consequently, many patients in real-life settings receive fewer anti-VEGF injections than administered in clinical trials, despite dosing recommendations in the regulatory-approved product label, with potentially fewer monitoring visits often resulting in suboptimal outcomes [11], leading to non-adherence and non-persistence to long-term therapy [12].

To address these real-world challenges, we introduce a new concept of “sustained disease control”, which is characterized by three inter-related goals of maintaining vision gains, rapid and resilient fluid control without clinically meaningful fluctuation, and with extended treatment intervals. We suggest this will address the treatment burden associated with frequent injections and/or monitoring visits, while maintaining the benefits of anti-VEGF therapy. The inter-relationship between these three factors is particularly evident in nAMD, where restoration and consistent stabilization of retinal fluid supports achievement and maintenance of vision gains and allows treatment interval extensions, while unchecked fluid recurrence can lead to suboptimal visual outcomes [13].

Previous studies have demonstrated that increased anti-VEGF doses may result in improved anatomic outcomes (aflibercept 0.5 to 4 mg) [14] or increased durability (ranibizumab 0.5 to 2 mg)

[15]. Recently, newer treatment options for nAMD (brolucizumab, faricimab and aflibercept 8 mg) have demonstrated non-inferior vision gains versus aflibercept 2 mg (the standard of care) [16–18]. More specifically, increasing the aflibercept dose from 2 mg to 8 mg aims to reduce treatment burden by providing a 4-fold higher molar dose, hypothesized to prolong ocular VEGF inhibition [19]. The available evidence on functional and anatomic outcomes and extended treatment intervals suggests that aflibercept 8 mg is able to deliver sustained disease control in a substantial proportion of patients (Table 1) [18, 20].

Aflibercept 8 mg is approved for the treatment of nAMD, DR, and DMO in various geographies based on robust clinical trial data. Firstly, aflibercept 8 mg was evaluated in the controlled phase 2, 44-week CANDELA study in 106 patients with nAMD where the safety profiles of aflibercept 8 mg and 2 mg, administered using the same dosing schedule (3 monthly injections followed by doses at Weeks 20 and 32, unless additional injections were warranted), were comparable [21]. In that data set, aflibercept 8 mg showed numerically greater anatomic and visual improvements compared with aflibercept 2 mg [21], with more patients without fluid in the central subfield at Week 16 [21]. Further, 3 pivotal trials are investigating the efficacy and safety of extended dosing with aflibercept 8 mg compared with aflibercept 2 mg every 8 weeks (2q8) in nAMD and DMO, or aflibercept 2 mg every 4 weeks in RVO [18, 20, 22]. QUASAR (NCT05850520) is a currently underway phase 3 study in patients with macular oedema secondary to RVO [22], while patients in the phase 3 study in nAMD (PULSAR: NCT04423718) and phase 2/3 study in DMO (PHOTON: NCT04429503) have completed masked 96-week treatment and are in the open-label extension phase [17, 20].

PULSAR and PHOTON used an algorithm in which treatment intervals could be modified if protocol-defined dose regimen modification (DRM) criteria were met [18, 20]. The dosing intervals for patients in the groups receiving aflibercept 8 mg every 12 (8q12) or 16 weeks (8q16) could be shortened from Week 16 (if DRM criteria denoting disease activity were met at any dosing visit; minimum dosing interval of 8 weeks) and extended from Week 52 (if both functional and anatomic DRM stability criteria compared with Week 12 were met) [18, 20].

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**Table 1.** Clinical trial evidence for aflibercept 8 mg in nAMD and DME.

Category	Evidence
Vision gains maintained	<p><b>PULSAR:</b></p> <ul style="list-style-type: none"> <li>Primary endpoint: LS mean change from baseline in BCVA letter score at Week 48 was +6.7 in the aflibercept 8q12 group, +6.2 in the 8q16 group, and +7.6 in the aflibercept 2q8 group. The estimated difference in LS mean changes (95% CI; confirmatory non-inferiority test at 4-letter margin) from baseline to Week 48 in BCVA letter score for aflibercept 8q12 vs 2q8 was -0.97 (-2.87 to 0.92; <math>p = 0.0009</math>) and for aflibercept 8q16 vs 2q8 was -1.14 (-2.97 to 0.69; <math>p = 0.0011</math>) [18].</li> <li>LS mean change from baseline in BCVA letter score at Week 96 was +5.6 in the aflibercept 8q12 group, +5.5 in the 8q16 group, and +6.6 in the aflibercept 2q8 group. The estimated difference in LS mean changes (95% CI; nominal non-inferiority test at 4-letter margin) from baseline to Week 96 in BCVA letter score for aflibercept 8q12 vs 2q8 was -1.01 (-2.82 to 0.80; <math>p = 0.0006</math> [nominal]) and for aflibercept 8q16 vs 2q8 was -1.08 (-2.87 to 0.71; <math>p = 0.0007</math> [nominal]) [24].</li> </ul> <p><b>PHOTON:</b></p> <ul style="list-style-type: none"> <li>Primary endpoint: LS mean change from baseline in BCVA letter score at Week 48 was +8.8 in the aflibercept 8q12 group, +7.9 in the 8q16 group, and +9.2 in the aflibercept 2q8 group. The estimated difference in LS mean changes (95% CI; confirmatory non-inferiority test at 4-letter margin) from baseline to Week 48 in BCVA letter score for 8q12 vs 2q8 was -0.57 (-2.26 to 1.13; <math>p &lt; 0.0001</math>) and for aflibercept 8q16 vs 2q8 -1.44 (-3.27 to 0.39; <math>p = 0.0031</math>) [20].</li> <li>LS mean change from baseline in BCVA letter score at Week 96 was +8.2 in the aflibercept 8q12 group, +6.6 in the 8q16 group, and +7.7 in the aflibercept 2q8 group. The estimated difference in LS mean changes (95% CI; nominal non-inferiority test at 4-letter margin) from baseline to Week 96 in BCVA letter score for aflibercept 8q12 vs 2q8 was +0.5 (-1.6 to 2.5; <math>p &lt; 0.0001</math> [nominal]) and for aflibercept 8q16 vs 2q8 was -1.1 (-3.3 to 1.1; <math>p = 0.0044</math> [nominal]) [23].</li> </ul>
Anatomic results	<p><b>PULSAR:</b></p> <ul style="list-style-type: none"> <li>Aflibercept 8 mg demonstrated a numerically faster median time to fluid-free central subfield vs aflibercept 2 mg (4 weeks with each aflibercept 8q12 and 8q16 groups vs 8 weeks with aflibercept 2 mg) [25].</li> <li>Key secondary endpoint: The pooled aflibercept 8 mg group showed statistically significant superiority vs aflibercept 2 mg in the proportion of patients with no retinal fluid in the center subfield at Week 16: 422 (63%) of 667 vs 173 (52%) of 335, respectively, with a treatment difference of 12% (95% CI: 5 to 18%; superiority test <math>p = 0.0002</math>) in favor of aflibercept 8 mg [18].</li> <li>Aflibercept 8 mg demonstrated a similar change in CRT to aflibercept 2 mg through Week 96. LS mean change in CRT from baseline to Week 48 was -147 <math>\mu\text{m}</math>, -147 <math>\mu\text{m}</math> and -136 <math>\mu\text{m}</math> in the aflibercept 8q12, 8q16, and 2q8 groups, respectively [18]. At Week 96, mean change in CRT from baseline was -152 <math>\mu\text{m}</math>, -149 <math>\mu\text{m}</math>, and -147 <math>\mu\text{m}</math> in the aflibercept 8q12, 8q16, and 2q8 groups, respectively [24].</li> </ul> <p><b>PHOTON:</b></p> <ul style="list-style-type: none"> <li>Aflibercept 8 mg demonstrated a similar change in CRT to aflibercept 2 mg through Week 96. Mean change in CRT from baseline to Week 48 was -171 <math>\mu\text{m}</math>, -148 <math>\mu\text{m}</math>, and -165 <math>\mu\text{m}</math> in the aflibercept 8q12, 8q16, and 2q8 groups, respectively [20]. At Week 96, mean change in CRT from baseline was -185 <math>\mu\text{m}</math>, -155 <math>\mu\text{m}</math>, and -187 <math>\mu\text{m}</math> for the aflibercept 8q12, 8q16, and 2q8 groups, respectively [23].</li> </ul>
Extended treatment intervals	<p><b>PULSAR:</b></p> <ul style="list-style-type: none"> <li>Overall, 88%, 71%, and 47% of patients receiving aflibercept 8 mg had assigned <math>\geq 12</math>-week, <math>\geq 16</math>-week, and <math>\geq 20</math>-week dosing intervals at Week 96 [24]. <ul style="list-style-type: none"> <li>In the aflibercept 8q16 group, 53% of patients had <math>\geq 20</math>-week and 31% had 24-week dosing intervals at Week 96 [24].</li> </ul> </li> <li>Patients received ~8 injections in the aflibercept 8q16 group vs ~13 injections in the aflibercept 2q8 group through Week 96 [24].</li> </ul> <p><b>PHOTON:</b></p> <ul style="list-style-type: none"> <li>Overall, 93%, 72%, and 44% of patients receiving aflibercept 8 mg had assigned <math>\geq 12</math>-week, <math>\geq 16</math>-week, and <math>\geq 20</math>-week dosing intervals at Week 96 [23]. <ul style="list-style-type: none"> <li>In the aflibercept 8q16 group, 46% of patients had <math>\geq 20</math>-week and 32% had 24-week dosing intervals at Week 96 [23].</li> </ul> </li> <li>During the initial treatment phase, the aflibercept 8 mg groups received 3 vs 5 initial monthly injections with aflibercept 2 mg [20].</li> <li>Patients received ~8 injections in the aflibercept 8q16 group vs ~14 injections in the aflibercept 2q8 group through Week 96 [23].</li> </ul>

2q8, 2 mg every 8 weeks; 8q12, 8 mg every 12 weeks; 8q16, 8 mg every 16 weeks; BCVA, best correct visual acuity; CI, confidence interval; CRT, central subfield retinal thickness; LS, least squares.

In both PULSAR and PHOTON, the primary endpoint of non-inferior visual gains with aflibercept 8 mg versus aflibercept 2 mg at Week 48 were met, with visual acuity improvements maintained through 96 weeks [23, 24]. The similar vision gains were achieved and maintained over 96 weeks with ~8 injections

in the aflibercept 8 mg arms of both studies and ~13 (PULSAR) or ~14 (PHOTON) injections in the aflibercept 2 mg arm [18, 20]. Overall, 53% and 47% of patients initially randomized to aflibercept 8q16 in PULSAR and PHOTON, respectively, had last assigned treatment intervals of at least 20 weeks [23, 24]. In

PULSAR, aflibercept 8 mg demonstrated superior drying compared with aflibercept 2 mg at Week 16, a key secondary endpoint for the trial [18], as well as rapid fluid control, with a numerically faster median time to fluid-free central subfield versus aflibercept 2 mg and fluid control maintained at Week 96 [18, 24, 25]. In both PULSAR and PHOTON, aflibercept 8 mg demonstrated a similar change in central retinal thickness to aflibercept 2 mg at Week 96 [23, 24]. Finally, the safety results of aflibercept 8 mg were comparable to the well-established safety profile of aflibercept 2 mg [23, 24].

Taken together, these findings provide support that aflibercept 8 mg can deliver sustained disease control in a substantial proportion of patients with nAMD or DMO through 96 weeks, with extended treatment intervals [18, 20]. While some patients may still require more frequent treatment, aflibercept 8 mg offers an opportunity for clinicians to meaningfully extend treatment intervals for most patients while maintaining vision gains and fluid control.

## DATA AVAILABILITY

All data generated or analysed during this study are included in this published article.

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## ADDITIONAL INFORMATION

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