Intravitreal Aflibercept 8 mg Injection in Patients With Neovascular Age-Related Macular Degeneration: 48-Week Results From the Phase 3 PULSAR Trial

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PURPOSE

To evaluate the efficacy and safety of intravitreal aflibercept 8 mg injection administered every 12 (8q12) or 16 weeks (8q16) versus aflibercept 2 mg every 8 weeks (2q8), each after three initial monthly injections in patients with treatment-naïve neovascular age-related macular degeneration (nAMD).

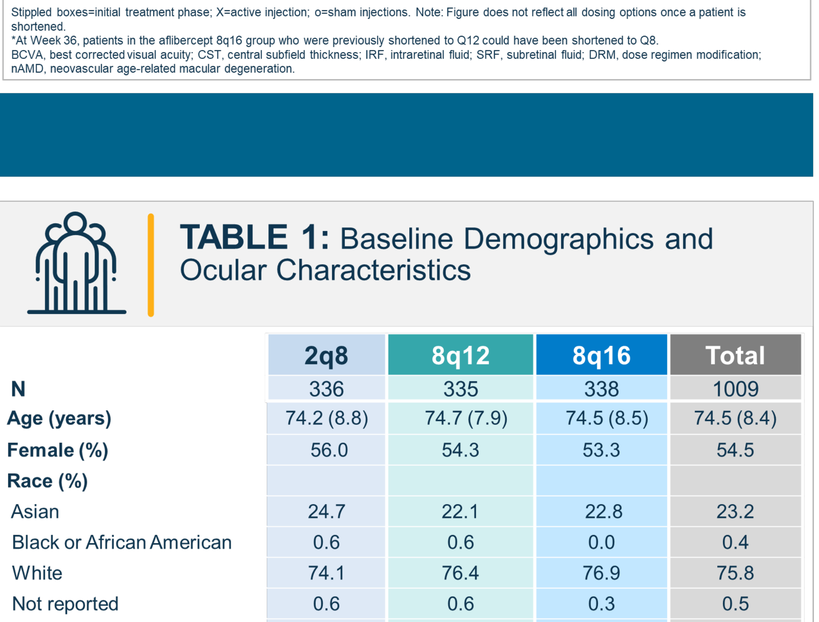
METHODS

PULSAR (NCT04423718) is an ongoing, double-masked, 96-week, Phase 3 trial: patients aged ≥50 years with nAMD were randomly assigned 1:1:1 to receive aflibercept 8 mg (70 µL injection) every 12 or 16 weeks (8q12 or 8q16), or aflibercept 2 mg (50 µL) every 8 weeks (2q8), each after three initial monthly injections (**Figure 1**).

In Year 1, from Week 16, treatment intervals could be shortened to a minimum of 8 weeks in the 8q12 or 8q16 groups if the patient met the dose regimen modification criteria (**Figure 1**).

Primary endpoint was mean best corrected visual acuity (BCVA) change from baseline at Week 48 (non-inferiority margin at four letters). The key secondary endpoint was proportion of patients with no intraretinal/subretinal fluid (IRF/SRF) in the center subfield at Week 16. Other secondary endpoints included safety. Exploratory endpoints included the proportion of patients with ≥12-week and 16-week treatment intervals through Week 48.

FIGURE 1: (A) PULSAR Study Design and (B) Dosing Schedule



	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Stippled boxes=initial treatment phase; X=active injection; o=sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
*At Week 36, patients in the aflibercept 8q16 group who were previously shortened to Q12 could have been shortened to Q8.
BCVA, best corrected visual acuity; CST, central subfield thickness; IRF, intraretinal fluid; SRF, subretinal fluid; DRM, dose regimen modification; nAMD, neovascular age-related macular degeneration.

RESULTS

Overall, 1009 patients (8q12: n=335; 8q16: n=338; 2q8: n=336) were evaluated (mean±SD age, 74.5±8.4 years; 54.5% female [**Table 1**]). Mean±SD BCVA at baseline was 59.9±13.4, 60.0±12.4, and 58.9±14.0 letters in the aflibercept 8q12, 8q16, and 2q8 groups, respectively.

The primary endpoint of non-inferiority was met with aflibercept 8 mg (8q12 vs 2q8: p=0.0009; 8q16 vs 2q8: p=0.0011). Observed mean±SD change from baseline in BCVA at Week 48 was +6.7±12.6, +6.2±11.7, and +7.6±12.2 letters in the aflibercept 8q12, 8q16, and 2q8 groups, respectively (**Figure 2**).

Aflibercept 8 mg demonstrated superior drying versus aflibercept 2 mg at Week 16; 63% versus 52% of patients had no IRF/SRF in the center subfield (p=0.0002 [**Figure 3**]). Median time to fluid-free center subfield was 4 weeks in both aflibercept 8 mg groups (**Figure 4**).

Observed mean±SD change in central subfield thickness from baseline to Week 48 was –142±120 µm, –147±131 µm, and –126±124 µm in the aflibercept 8q12, 8q16, and 2q8 groups, respectively.

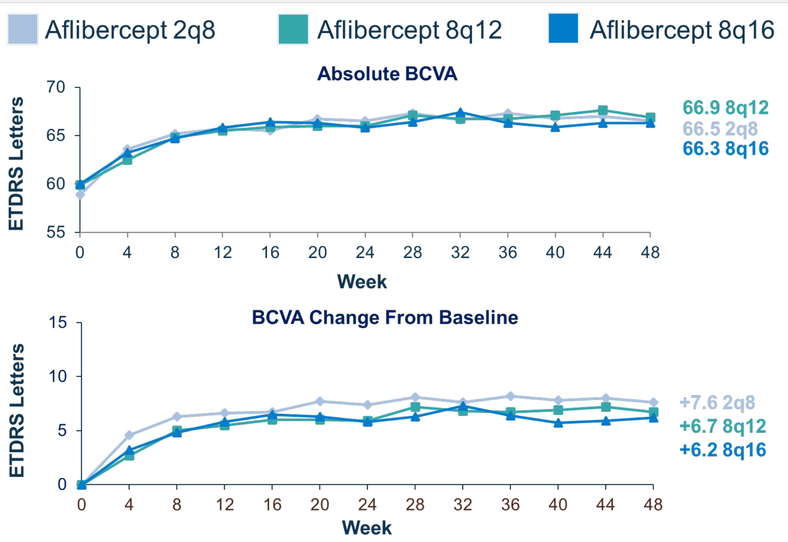
In the 8q12 group, 79% of patients (n=316) maintained 12-week dosing intervals and 77% of patients (n=312) in the 8q16 group maintained 16-week dosing intervals in Year 1 after the initial monthly dosing period. Overall, 83% of patients (n=628) receiving aflibercept 8 mg maintained ≥12-week dosing intervals in Year 1 (**Figure 5**). The safety profile of aflibercept 8 mg was similar to that of aflibercept 2 mg (**Table 2**).

TABLE 1: Baseline Demographics and Ocular Characteristics

	2q8	8q12	8q16	Total
N	336	335	338	1009
Age (years)	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.5 (8.4)
Female (%)	56.0	54.3	53.3	54.5
Race (%)				
Asian	24.7	22.1	22.8	23.2
Black or African American	0.6	0.6	0.0	0.4
White	74.1	76.4	76.9	75.8
Not reported	0.6	0.6	0.3	0.5
Ethnicity (%)				
Hispanic or Latino	3.6	2.1	2.7	2.8
Hypertension (%)	60.7	66.3	64.8	63.9
BCVA (ETDRS letters)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.6 (13.3)
Snellen equivalent	20/63	20/63	20/63	20/63
20/32 (74–78 letters, %)	14.6	12.5	14.2	13.8
20/40 or worse (≤73 letters, %)	85.4	87.5	85.8	86.2
CST (µm)	367 (134)	370 (124)	371 (133)	369 (130)
Total lesion area (as per reading center, mm²)	6.9 (5.4)	6.4 (5.1)	6.9 (5.7)	6.7 (5.4)
CNV classification (as per reading center, %)				
Predominantly classic	21.1	21.2	19.8	20.7
Minimally classic	18.2	16.7	20.1	18.3
Occult	57.1	58.8	55.0	57.0

FAS. Data are mean (SD) unless otherwise indicated.
BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set.

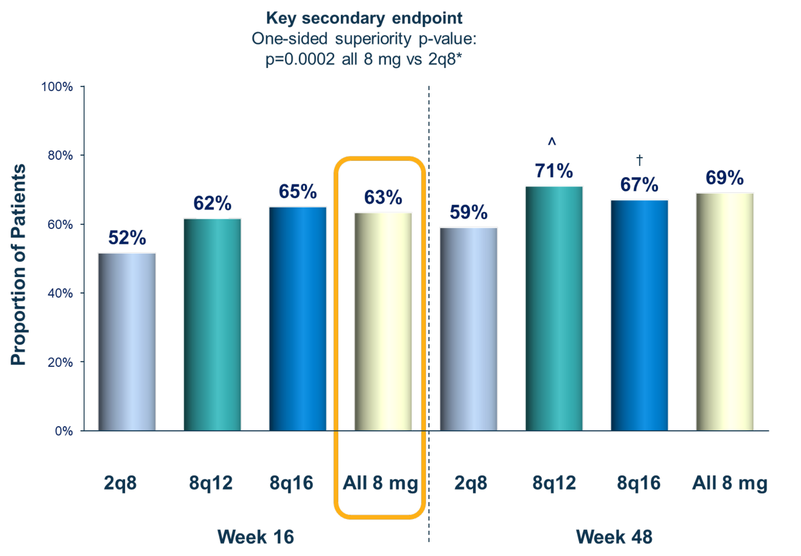
FIGURE 2: Mean BCVA Change From Baseline Through Week 48



	LS mean change from baseline at Week 48 (MMRM)	Difference in LS means vs 2q8	Two-sided 95% CI	One-sided test for non-inferiority at four-letter margin
2q8	7.0	—	—	—
8q12	6.1	−0.97	−2.87, 0.92	p=0.0009
8q16	5.9	−1.14	−2.97, 0.69	p=0.0011

Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
BCVA, best corrected visual acuity; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measurements.

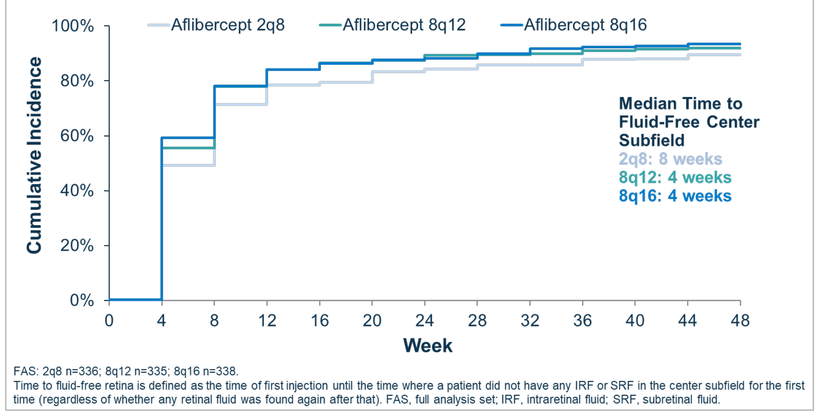
FIGURE 3: Proportion of Patients Without Retinal Fluid in Center Subfield at Weeks 16 and 48



Without retinal fluid defined as absence of IRF and SRF in center subfield.
LOCF (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
*P-value: one-sided Cochran–Mantel–Haenszel; weighting scheme adjusted by geographical region and baseline BCVA (<60 vs ≥60). ^Nominal p=0.0015 8q12 vs 2q8. †Nominal p=0.0458 8q16 vs 2q8.
BCVA, best corrected visual acuity; FAS, full analysis set; ICE, intercurrent event; IRF, intraretinal fluid; LOCF, last observation carried forward, SRF, subretinal fluid.

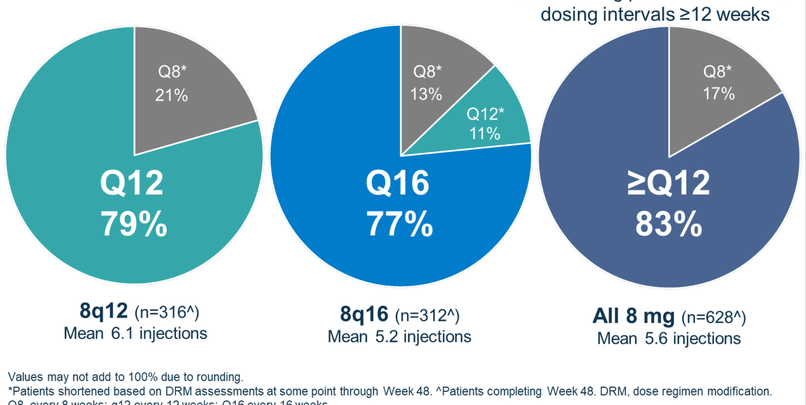
RESULTS

FIGURE 4: Time to Fluid-Free Center Subfield



FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
Time to fluid-free retina is defined as the time of first injection until the time where a patient did not have any IRF or SRF in the center subfield for the first time (regardless of whether any retinal fluid was found again after that). FAS, full analysis set; IRF, intraretinal fluid; SRF, subretinal fluid.

FIGURE 5: Proportion of Patients Who Maintained Randomized Intervals Through Week 48



Values may not add to 100% due to rounding.
*Patients shortened based on DRM assessments at some point through Week 48. ^Patients completing Week 48. DRM, dose regimen modification. Q8, every 8 weeks; q12 every 12 weeks; Q16 every 16 weeks.

TABLE 2: Safety Through Week 48

	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥1 ocular AE in the study eye (%)	38.7	38.5	37.6	38.0
AEs occurring in ≥2% of patients in any group				
Cataract	3.0	3.6	3.6	3.6
Intraocular pressure increased	2.1	3.3	2.7	3.0
Retinal hemorrhage	4.2	3.3	3.0	3.1
Subretinal fluid	3.3	3.0	1.5	2.2
Visual acuity reduced	6.0	3.6	5.3	4.5
Vitreous floaters	3.3	1.2	3.6	2.4
Patients with ≥1 IOI TEAE (%)	0.6	1.2	0.3	0.7
Patients with IOP ≥35 mmHg pre- or post-injection (%)	0.3	0.9	0.3	0.6
Patients with ≥1 non-ocular AE (%)				
APTC events*	1.5	0.3	0.3	0.3
Hypertension events*	3.6	4.8	4.7	4.8
Non-ocular SAEs*	13.7	10.1	9.5	9.8
Deaths^	1.5	0.9	0.3	0.6

No cases of ischemic optic neuropathy were reported through Week 48.

*Treatment-emergent events. ^All events.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; IOP, intraocular pressure; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

CONCLUSIONS

Aflibercept 8 mg met the primary efficacy endpoint in nAMD at Week 48, demonstrating non-inferiority in BCVA change versus aflibercept 2 mg. At Week 16, there was a significantly greater proportion of patients who had no fluid in the center subfield in the combined aflibercept 8 mg group versus the aflibercept 2 mg group (63% vs 52%). The superior drying effect of aflibercept 8 mg was maintained numerically through Week 48.

Through Week 48, 79% and 77% of the patients in the 8q12 and 8q16 groups maintained their original randomized dosing interval; 83% of the combined aflibercept 8 mg maintained ≥12-week dosing intervals. Overall, these findings suggest that aflibercept 8 mg may provide greater therapeutic benefit with longer dosing intervals, and equivalent safety versus aflibercept 2 mg.

Disclosures

Justus G. Garweg: Consultant for AbbVie, Bayer, Novartis, and Roche.
Financial support: The PULSAR study was sponsored by Bayer AG (Leverkusen, Germany) and co-funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this abstract.

Study disclosure

This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation.

Acknowledgments

Medical writing support, under the direction of the author, was provided by ApotheCom and funded by Bayer Consumer Care AG (Basel, Switzerland), in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med.* 2022;175:1298–1304). The results of the PULSAR study were previously presented at The Retina Society 55th Annual Scientific Meeting, November 2–5, 2022; Angiogenesis, February 10–11, 2023; The 46th Annual Macular Society Meeting, February 15–18, 2023; FujiRetina, March 23–25, 2023; ARVO Annual Meeting, April 23–27, 2023; and the ASRS Annual Meeting, July 28–August 1, 2023.

Presented at Schweizerische Ophthalmologische Gesellschaft (SOG) Congress, Lausanne, Switzerland [August 30–September 1, 2023]