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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INTRODUCTION

- Aflibercept 8 mg, a novel intravitreal formulation that delivers a 4-times higher molar dose than aflibercept 2 mg, has demonstrated improved functional and anatomic outcomes at dosing intervals of ≥12 weeks in ongoing clinical trials
- These findings supported regulatory approval of aflibercept 8 mg for the treatment of neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and diabetic retinopathy (DR) in the United States[1]
- Herein, 48-week results are reported from the 96-week, randomized, double-masked, Phase 3 PULSAR (NCT04423718) trial evaluating the efficacy and safety of aflibercept 8 mg versus 2 mg in patients with treatment-naive nAMD

METHODS

- Eligible patients with treatment-naive nAMD (**Table 1**) were randomized 1:1:1 to receive aflibercept 8 mg every 12 or 16 weeks (8q12 or 8q16), or aflibercept 2 mg every 8 weeks (2q8), following three initial monthly injections (**Figure 1A**)
- Starting at Week 16, randomized dosing intervals of patients in the aflibercept 8q12 and 8q16 groups were shortened if dose regimen modification (DRM) criteria were met (**Figure 1B**)

Table 1. Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Men or women ≥50 years of age with treatment-naïve nAMD • Active subfoveal CNV, with a total area >50% of the total lesion area in the study eye • Presence of IRF and/or SRF in the central subfield on OCT • BCVA of 78–24 ETDRS letters (Snellen equivalent 20/32–20/320) with decreased vision due to nAMD	• DR, DME, or any retinal vascular disease other than nAMD in either eye • Retinal pigment epithelial tears or rips, scar, fibrosis, or atrophy involving the central subfield in the study eye • Total lesion size >12-disc areas (30.5 mm^2, including blood, scars, and neovascularization) as assessed by FA in the study eye • Uncontrolled glaucoma (IOP >25 mmHg despite anti-glaucoma medication) in the study eye • Extra/periocular infection or inflammation in either eye at screening or randomization • Uncontrolled blood pressure (SBP >160 mmHg or DBP >95 mmHg)

BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; DBP, diastolic blood pressure; ETDRS, Early Treatment of Diabetic Retinopathy Study; FA, fundus angiogram; IOP, intraocular pressure; IRF, intraretinal fluid; OCT, optical coherence tomography; SBP, systolic blood pressure; SRF, subretinal fluid.

Figure 1. (A) PULSAR Study Design and (B) Dosing Schedule

(A)

Multicenter, randomized, double-masked study in patients with treatment-naïve nAMD
Randomized at baseline 1 (2q8) : 1 (8q12) : 1 (8q16)

- **2q8** Aflibercept 2 mg every 8 weeks after 3 initial monthly injections n=336
- **8q12** Aflibercept 8 mg every 12 weeks after 3 initial monthly injections n=335
- **8q16** Aflibercept 8 mg every 16 weeks after 3 initial monthly injections n=338

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)
Key secondary endpoint at Week 16
Proportion of patients without IRF and SRF in the center subfield

End of study at Week 96 with optional 1-year extension through Week 156

(B)

	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 (Primary Endpoint)
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o[a]	X[a]	o	o	X[a]	o	o	X[a]	o
8q16	X	X	X	o	o[a]	o[a]	X[a]	o	o	o	X[a]	o	o

DRM criteria for shortening dosing interval[b]
- >5-letter loss in BCVA due to persistent or worsening nAMD
- AND
- >25-µm increase in CRT, new-onset foveal neovascularization, or foveal hemorrhage

DRM in Year 1
- Intervals can only be shortened → **Week 16 and 20:** Patients on 8q12 and 8q16 meeting DRM criteria were shortened to Q8
- Multiple opportunities to shorten interval → **Week 24:** Patients on 8q16 meeting DRM criteria were shortened to Q12
- Minimum interval for all patients was Q8 → **Week 32 and 44 for 8q12 and Week 40 for 8q16:** Treatment interval was shortened by 4 weeks for patients meeting DRM criteria

Stippled boxes=initial treatment phase; X=active injection; o=sham injections.
Note: Figure does not reflect all dosing options once a patient is shortened.
[a]Shortening of dosing interval was permitted for patients meeting prespecified DRM criteria. [b]All assessments compared to Week 12.
CRT, central retinal thickness.

RESULTS

- The overall study completion rate at Week 48 was 93.3%
- Baseline demographics and ocular characteristics were similar across treatment arms (**Table 2**)

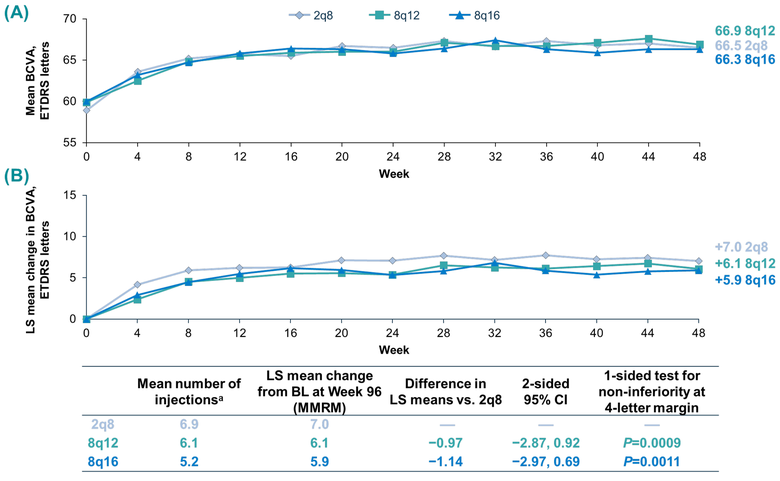
Table 2. Baseline Demographics and Ocular Characteristics

	2q8 (n=336)	8q12 (n=335)	8q16 (n=338)	Total (N=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
White (%)	74.1	76.4	76.9	75.8
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
CRT (µm)	367 (134)	370 (124)	371 (133)	369 (130)
Total lesion area (as per reading center, mm^2)	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.
FAS, full analysis set.

- The primary endpoint was met in both aflibercept 8-mg groups, with 8q12 and 8q16 demonstrating non-inferior BCVA gains to 2q8 at Week 48 (**Figure 2**)

Figure 2. (A) Absolute BCVA and (B) LS Mean BCVA Change From Baseline Through Week 48

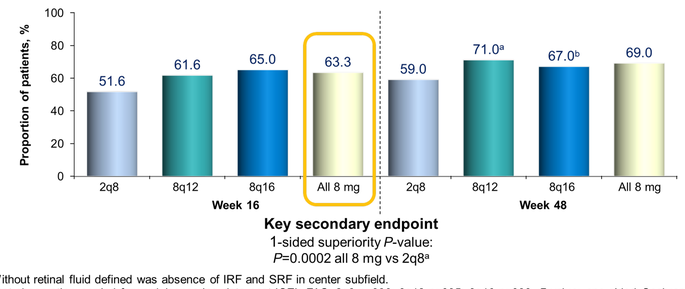


	Mean number of injections[a]	LS mean change from BL at Week 96 (MMRM)	Difference in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	6.9	7.0	—	—	—
8q12	6.1	6.1	−0.97	−2.87, 0.92	*P*=0.0009
8q16	5.2	5.9	−1.14	−2.97, 0.69	*P*=0.0011

Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
LS mean change was generated using MMRM, with baseline BCVA as a covariate, treatment group (2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world] and baseline BCVA [<60 vs ≥60 ETDRS letters]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit.
ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measurements.

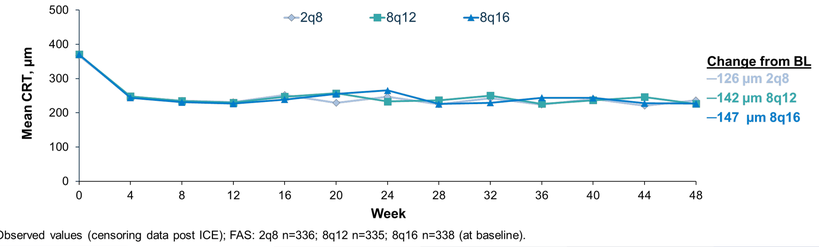
- Aflibercept 8 mg demonstrated superior drying versus aflibercept 2 mg at Week 16 (**Figure 3**)
- Absolute CRT was similar across all 3 treatment groups, with minimal fluctuations through Week 48 (**Figure 4**)

Figure 3. Proportion of Patients Without Retinal Fluid in Center Subfield at Weeks 16 and 48



Without retinal fluid defined was absence of IRF and SRF in center subfield.
Last observation carried forward (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 ETDRS letters).
[a]Nominal *P*=0.0015 for 8q12 vs 2q8. [b]Nominal *P*=0.0458 for 8q16 vs 2q8.

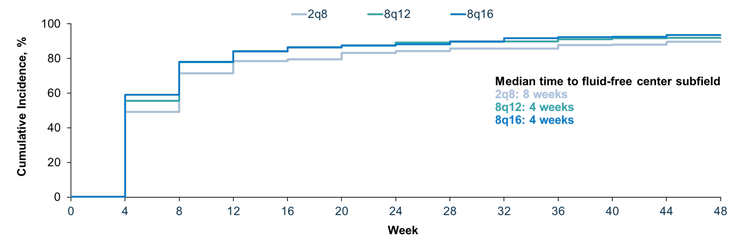
Figure 4. Absolute CRT Through Week 48



Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).

- Median time to fluid-free center subfield was 4 weeks with 8q12 and 8q16 versus 8 weeks for 2q8 (**Figure 4**)

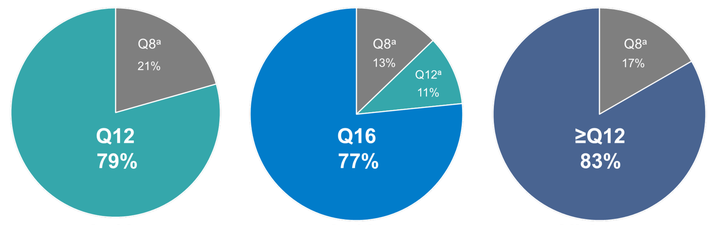
Figure 4: Time to Fluid-Free Center Subfield



FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
Time to fluid-free retina was 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).

- Through Week 48, 83% of patients receiving aflibercept 8 mg maintained ≥12-week dosing interval through Week 48 (**Figure 5**)

Figure 5. Proportion of Patients Who Maintained Randomized Intervals Through Week 48



Values may not add to 100% due to rounding.
[a]Patients with dosing intervals that were shortened based on DRM assessments at some point through Week 48.
[b]Patients completing Week 48.

- Safety of aflibercept 8 mg was consistent with the established safety profile of aflibercept 2 mg (**Table 3**)
  - No cases of ischemic optic neuropathy, retinal vasculitis, or occlusive retinitis were reported through Week 48
  - Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 96 in any treatment group

Table 3. Safety Through Week 48

	2q8 (n=336)	8q12 (n=335)	8q16 (n=338)
Ocular safety			
Patients with ≥1 ocular AE (%)[a]	38.7	38.5	37.6
Patients with ≥1 IOI AE (%)[a]	0.6	1.2	0.3
Patients with IOP ≥35 mmHg pre- or post-injection (%)[b]	0.3	0.9	0.3
Non-ocular safety			
APTC events (%)[a]	1.5	0.3	0.3
Hypertension events (%)[a]	3.6	4.8	4.7
Non-ocular SAEs (%)[a]	13.7	10.1	9.5
Deaths (%)[c]	1.5	0.9	0.3

SAF. [a]Treatment emergent. [b]IOP was measured in the study eye. [c]All events.
APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; SAE, serious adverse event; SAF, safety analysis set.

CONCLUSIONS

- Aflibercept 8 mg demonstrated non-inferiority BCVA versus aflibercept 2 mg through Week 48, with 83% of patients in the combined 8-mg group maintaining ≥12-week dose intervals
- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 48 weeks

REFERENCE

1. EYLEA® HD (aflibercept) injection, for intravitreal use. Highlights of prescribing information. Regeneron Pharmaceuticals, Inc.; 2023. Accessed September 14, 2023. https://www.regeneron.com/downloads/eyleahd_fpi

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