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Rapid fluid resolution with aflibercept 8 mg may be associated with extended dosing intervals at Week 96 in nAMD: A PULSAR post hoc analysis

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Purpose

- This analysis of the PULSAR Phase 3 trial evaluated whether early fluid resolution (no intraretinal fluid [IRF] and no subretinal fluid [SRF]) in the central subfield was associated with last assigned dosing interval at Week 96 in patients treated with aflibercept 8 mg

Conclusions

- **Rapid fluid resolution** during the initial monthly treatment period **may be associated with extended dosing intervals** in patients who received aflibercept 8 mg for nAMD at Week 96
- **Fluid resolution at Week 4** after 1 injection may be associated with **extended dosing intervals**
- Patients who had early fluid resolution can achieve extended dosing intervals **without compromising visual and anatomic outcomes**

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Methods

- PULSAR (NCT04423718) was a double-masked, 96-week, Phase 3 trial in patients aged ≥50 years with treatment-naïve neovascular age-related macular degeneration (nAMD). Patients were randomly assigned 1:1:1 to receive intravitreal aflibercept 8 mg every 12 weeks (8q12 [n=335]), every 16 weeks (8q16 [n=338]), or aflibercept 2 mg every 8 weeks (2q8; n=336), each after 3 initial monthly injections. Beginning at Week 16, dosing intervals in the 8q12 and 8q16 groups were modified if predefined criteria were met (**Figure 1**)
- The association between fluid resolution at Weeks 4, 8, and 12 (4 weeks after each initial monthly injection) and last assigned dosing interval at Week 96 in patients who received aflibercept 8 mg (the 8q12 and 8q16 groups) was analyzed (**Table 1**)

Figure 1: PULSAR – Dosing schedule and regimen modification in Years 1 and 2

	YEAR 1 (Week)													YEAR 2 (Week)											
	D1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96
2q8	X	X	X		X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	–
8q12	X	X	X		o[a]	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	–
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	–

[a]DRM: Interval shortening during Years 1 and 2

Criteria for interval shortening
- >5-letter loss in BCVA compared with Week 12 due to persistent or worsening nAMD **AND**
- >25 µm increase in CRT compared with Week 12, **OR** new foveal neovascularization, **OR** new foveal hemorrhage

- Patients who met DRM criteria had dosing intervals shortened to Q8 at **Weeks 16** and **20** or by 4-week increments from **Week 24**
  - The minimum assigned dosing interval was Q8

[b]DRM: Interval extension during Year 2

Criteria for interval extension
- <5-letter loss in BCVA compared with Week 12 **AND**
- No fluid at the central subfield on OCT **AND**
- No new foveal hemorrhage or foveal neovascularization

- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
  - The maximum assigned dosing interval was Q24

Figure does not reflect all dosing options once a patient's dosing interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injections. Qn, every n weeks; BCVA, best-corrected visual acuity; CRT, central retinal subfield thickness; D, day; DRM, dose regimen modification; OCT, optical coherence tomography; nAMD, neovascular age-related degeneration.

Table 1: Patient groups analyzed based on early fluid status up to Week 12

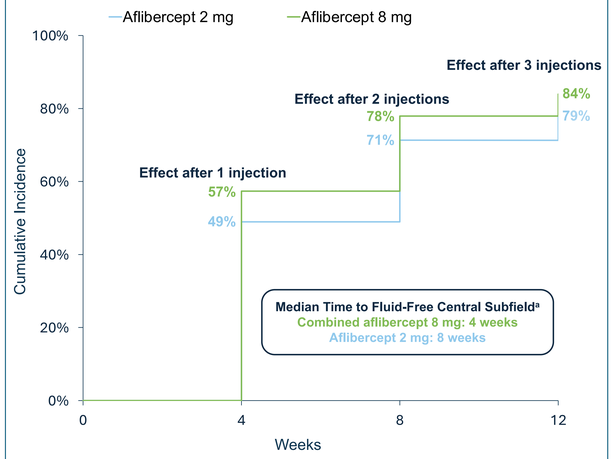
Fluid-free / Fluid present	D1	W4	W8	W12
Three initial monthly injections in both aflibercept 8 mg and 2 mg groups	💉	💉	💉	
Fluid-free at W4		💧		
Fluid-free at W4 and W8		💧	💧	
Fluid-free at W4, W8, and W12		💧	💧	💧
Fluid present at W4 and fluid-free at W8		💦	💧	
Fluid present at W4, W8, and W12		💦	💦	💦

Fluid status was not assessed on D1 but was evaluated pre-injection at W4 and W8. It was defined as the absence of intraretinal fluid and subretinal fluid (fluid-free) or the presence of fluid (fluid present) in the central subfield. Grey shading = fluid-free, not fluid-free, or unknown fluid status. BCVA, best-corrected visual acuity; CRT, central retinal subfield thickness; D, day; W, week.

Results

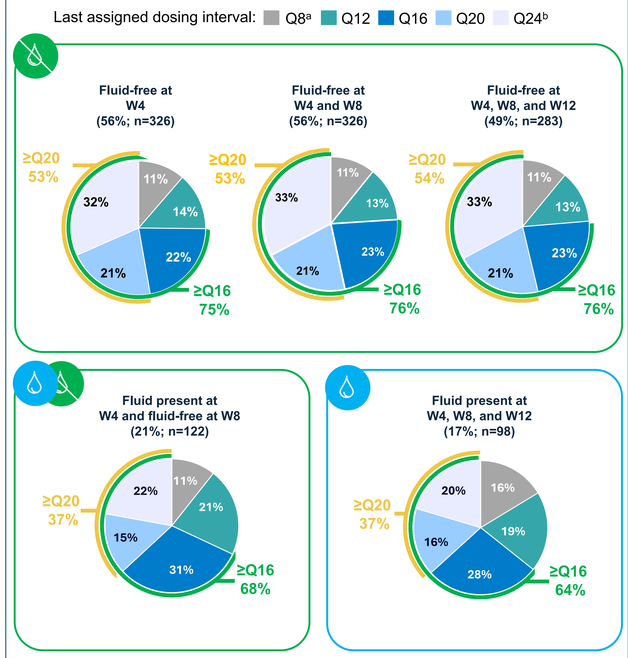
- Aflibercept 8 mg demonstrated a numerically faster median time to fluid-free central subfield than aflibercept 2 mg (4 weeks compared with 8 weeks, respectively; **Figure 2**)
- In the aflibercept 8 mg group, more patients who had fluid resolution after 1 injection had a last assigned dosing interval of ≥16 weeks and ≥20 weeks at Week 96 compared with those who had fluid present at Weeks 4, 8, and 12 (**Figure 3**)
- BCVA gains and CRT reductions at Week 16 were maintained over 96 weeks in treatment groups (**Table 2**)

Figure 2: Time to a fluid-free central subfield



FAS: aflibercept 2 mg group, n=336; aflibercept 8 mg groups, n=673. Time to fluid-free central subfield was defined as the time of first injection until the time when a patient had no intraretinal fluid or no subretinal fluid in the central subfield for the first time (regardless of whether any retinal fluid in the central subfield was found again later). [a]Time to fluid-free central subfield was analyzed using the Kaplan–Meier method, using the study visits (i.e. multiples of 4 weeks) and not the calendar time as unit. FAS, full analysis set.

Figure 3: Last assigned dosing interval at Week 96 of the combined aflibercept 8 mg groups by early fluid status



FAS. Data shown for patients who completed 96 weeks of treatment. Values may not add up to 100% due to rounding. [a]Patients shortened based on DRM assessments at some point through Week 96. [b]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period. DRM, dose modification regimen; FAS, full analysis set; Qn, every n weeks; W, week.

Table 2: BCVA and CRT outcomes of the combined aflibercept 8 mg groups through Week 96 by early fluid status

Patient groups	BCVA (ETDRS letters) Baseline	W16	W48	W96	CRT (µm) Baseline	W16	W48	W96
Fluid-free at W4	61.1±12.2 (n=385)	66.5±14.5 (n=374)	66.3±15.9 (n=330)	65.9±17.4 (n=299)	339±110 (n=385)	229±60 (n=372)	217±56 (n=325)	213±58 (n=294)
Fluid-free at W4 and W8	61.6±12.0 (n=346)	67.2±14.3 (n=340)	66.9±15.9 (n=298)	66.3±17.7 (n=270)	334±105 (n=346)	226±58 (n=338)	214±53 (n=294)	213±56 (n=267)
Fluid-free at W4, W8, and W12	61.8±11.9 (n=328)	67.4±14.2 (n=325)	67.0±16.0 (n=285)	66.3±17.9 (n=259)	333±105 (n=328)	226±58 (n=323)	215±52 (n=281)	213±56 (n=255)
Fluid present at W4 and fluid-free at W8	60.7±12.8 (n=135)	69.1±14.2 (n=132)	69.8±14.0 (n=125)	68.8±14.2 (n=108)	398±122 (n=135)	239±58 (n=129)	226±46 (n=123)	229±54 (n=105)
Fluid present at W4, W8, and W12	56.0±14.4 (n=102)	61.3±15.5 (n=100)	62.8±15.7 (n=94)	62.8±16.9 (n=82)	439±159 (n=102)	302±102 (n=96)	266±86 (n=87)	247±83 (n=78)

FAS. OC prior to ICE. Values are mean±standard deviation. BCVA, best-corrected visual acuity; CRT, central retinal subfield thickness; FAS, full analysis set; ETDRS, Early Treatment Diabetic Retinopathy Study; ICE, intercurrent event; OC, observed cases; W, week.

Disclosures

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