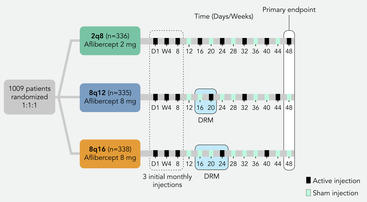
Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration (nAMD): 48-week results from the Phase 3 PULSAR trial

The Phase 3 PULSAR trial evaluated the safety and efficacy of intravitreal injections of 8 mg aflibercept in eyes with nAMD. This 4-times higher molar dose of aflibercept is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on vascular endothelial growth factor (VEGF) signaling. This global study is ongoing and conducted across 223 sites in 26 countries.

Korobelnik JF on behalf of the PULSAR study investigators. Presented at The Retina Society 55th Annual Scientific Meeting; November 2-5, 2022; Pasadena, CA.

Patients with treatment-naïve neovascular AMD were randomized and double-masked over a study period of 96 weeks, with primary endpoint at Week 48.



Dose Regimen

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

Dose Regimen Modifications (DRM) in Year 1

DRM criteria for shortening dosing interval:

>5-letter loss in BCVA from week 12 due to persistent or worsening nAMD

+

>25 µm increase in CRT from week 12 or new onset foveal neovascularization or foveal hemorrhage

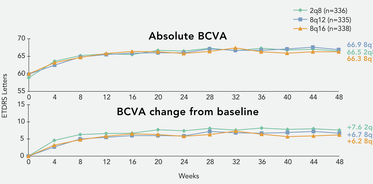
- **Weeks 16 or 20:** 8q12 or 8q16 patients meeting DRM criteria had treatment interval shortened **to every 8 weeks**
- **Week 24:** 8q16 patients meeting DRM criteria had treatment interval shortened **to every 12 weeks**
- **Subsequent dosing visits:** patients on 8 mg meeting DRM criteria had treatment interval shortened **by 4 weeks**

Analysis endpoints

- **Primary endpoint (Week 48):** mean change in BCVA (non-inferiority)
- **Key secondary endpoint (Week 16):** proportion of patients without IRF and SRF in center subfield
- End of study at Week 96

BCVA = best corrected visual acuity; nAMD = neovascular age-related macular degeneration; CRT = central retinal thickness; IRF = intraretinal fluid; SRF = subretinal fluid.

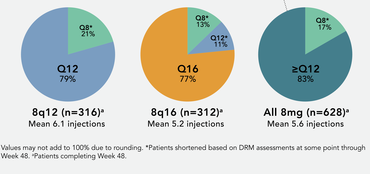
The BCVA primary endpoint was met in both 8 mg groups.



	Mean change from baseline at week 48 (MMRM)	Difference in mean vs. 2q8 (95% CI)	1-sided test for non-inferiority at 4-letter margin
2q8	7.0		
8q12	6.1	-0.97 (-2.87, 0.92)	*P*= .0009
8q16	5.9	-1.14 (-2.97, 0.69)	*P*= .0011

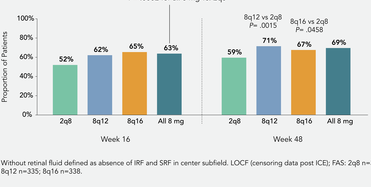
MMRM, mixed model for repeated measurements.

A large majority of 8 mg patients maintained Q12- & Q16-week intervals through week 48.



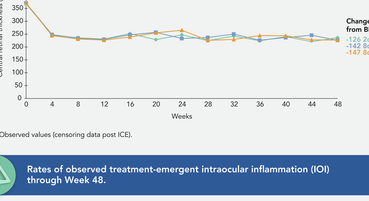
Values may not add to 100% due to rounding. *Patients shortened based on DRM assessments at some point through Week 48. aPatients completing Week 48.

The proportion of patients without retinal fluid in center subfield at weeks 16 and 48 was over 60% in both 8 mg groups.



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.

There was a change in central retinal thickness from baseline observed in all groups.



Observed values (censoring data post ICE).

Rates of observed treatment-emergent intraocular inflammation (IOI) through Week 48.

	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 IOI AE (%)*	0.6%	1.2%	0.3%	0.7%

*Treatment-emergent events.

Reported IOI terms: chorioretinitis, iridocyclitis, iritis, vitreal cells, vitritis.
No cases of endophthalmitis or occlusive retinal vasculitis were observed.

SAF = safety analysis set; IOI = intraocular inflammation; AE = adverse events.

PULSAR 48-week safety results.

Safety of aflibercept 8 mg consistent with established safety profile of aflibercept 2 mg

No new safety signals for aflibercept 8 mg or 2 mg and no cases of retinal vasculitis, occlusive retinitis or endophthalmitis

No evidence of increased IOP with aflibercept 8 mg

Incidence of APTC events was similar with aflibercept 8 mg and 2 mg

IOP = intraocular pressure; APTC = Anti-Platelet Trialists' Collaboration.

Conclusion

PULSAR Phase 3 **primary and key secondary endpoints were met,** with aflibercept 8q12 and 8q16 dose groups demonstrating non-inferior BCVA at 48 weeks as well as superior drying at Week 16 compared to 2q8 dose regimen, with comparable ocular/nonocular safety and randomized interval maintenance.