Pooled Safety Analysis of Aflibercept 8 mg for up to 96 Weeks in the CANDELA, PHOTON, and PULSAR Trials

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- These trials include research conducted on human patients. Institutional review board approval was obtained prior to initiation of all trials
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Background

- Aflibercept 8 mg is a novel formulation that delivers a 4-fold higher molar dose than aflibercept 2 mg, potentially suppressing VEGF signaling over a longer duration
- Aflibercept 8 mg demonstrated comparable efficacy and safety to aflibercept 2 mg in the proof-of-concept Phase 2 CANDELA trial in nAMD, the pivotal Phase 3 PULSAR trial in nAMD, and the pivotal Phase 3 PHOTON trial in DME[1-3]
- The present analysis, including >1200 patients who received >10,000 injections of aflibercept 8 mg over 2 years, was conducted to further assess safety with aflibercept 8 mg

This analysis evaluated the safety of aflibercept 8 mg and 2 mg for up to 96 weeks across the CANDELA, PULSAR, and PHOTON trials

DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Wykoff CC et al. *JAMA Ophthalmol*. 2023;141:834-842. 2. Lanzetta P et al. *Lancet*. 2024;403:1141-1152. 3. Brown DM et al. *Lancet*. 2024;403:1153-1163.

Study Designs

CANDELA

Phase 2, multi-center, randomized, single-masked study in patients with nAMD

- Aflibercept 2 mg[a] n=53
- Aflibercept 8 mg[a] n=53

Primary endpoint at Week 16
Proportion of patients without fluid in the center subfield

→ End of study at Week 44

PULSAR and PHOTON

Multi-center, randomized, double-masked studies in patients with nAMD (PULSAR) or DME (PHOTON)

- 2q8[b] n=336 (PULSAR) n=167 (PHOTON)
- 8q12[c] n=335 (PULSAR) n=328 (PHOTON)
- 8q16[d] n=338 (PULSAR) n=163 (PHOTON)

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

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

[a]Three initial monthly injections followed by injections at Weeks 20 and 32.
[b]Aflibercept 2 mg every 8 weeks after 3 (PULSAR) or 5 (PHOTON) initial monthly injections.
[c]Aflibercept 8 mg every 12 weeks after 3 initial monthly injections.
[d]Aflibercept 8 mg every 16 weeks after 3 initial monthly injections.
BCVA, best-corrected visual acuity.

Aflibercept Exposure Through Week 96

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Total number of injections	6464	10,067
Number of injections, mean (SD)	11.6 (3.1)	8.3 (2.1)
Treatment duration, mean (SD), weeks	84.1 (24.5)	86.8 (22.6)

SD, standard deviation

Ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Ocular TEAEs, n (%)	263 (47.3)	583 (47.9)
Ocular TEAEs in ≥3% of patients in any treatment group, n (%)		
Cataract[a]	53 (9.5)	140 (11.5)
Visual acuity reduced	30 (5.4)	53 (4.4)
Vitreous floaters	22 (4.0)	49 (4.0)
Conjunctival hemorrhage	17 (3.1)	46 (3.8)
Vitreous detachment	16 (2.9)	45 (3.7)
Retinal hemorrhage	22 (4.0)	44 (3.6)
Intraocular pressure increased	17 (3.1)	34 (2.8)
Subretinal fluid	17 (3.1)	24 (2.0)

- No cases of ischemic optic neuropathy were reported with aflibercept 8 mg, and 1 case of ischemic optic neuropathy was reported with aflibercept 2 mg through Week 96

[a]Includes cataract, cataract cortical, cataract nuclear, cataract operation, cataract subcapsular, lenticular opacities, and posterior capsule opacification although not all terms met the ≥3% threshold.

Intraocular Inflammation

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
IOI, n (%)	11 (2.0)	16 (1.3)
Iridocyclitis	2 (0.4)	4 (0.3)
Iritis	0	3 (0.2)
Anterior chamber cell	1 (0.2)	2 (0.2)
Uveitis	2 (0.4)	2 (0.2)
Vitreal cells	2 (0.4)	2 (0.2)
Vitritis	0	2 (0.2)
Chorioretinitis	0	1 (<0.1)
Endophthalmitis	2 (0.4)	0
Eye inflammation	1 (0.2)	0
Hypopyon	1 (0.2)	0

- Most IOI cases were non-serious and mild or moderate in severity
- No cases of occlusive retinal vasculitis were reported through Week 96 in any treatment group

IOI, intraocular inflammation

IOP in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
IOP increase ≥10 mmHg from baseline (pre-injection), n (%)[a]	15 (2.7)[b]	49 (4.0)[c]
IOP ≥35 mmHg pre- or post-injection, n (%)[a]	4 (0.7)[d]	6 (0.5)[e]

[a]At any visit.
[b]CANDELA (n=0), PULSAR (n=11), and PHOTON (n=5).
[c]CANDELA (n=2), PULSAR (n=18), PHOTON (n=28).
[d]CANDELA (n=0), PULSAR (n=2), and PHOTON (n=2).
[e]CANDELA (n=0), PULSAR (n=4), and PHOTON (n=2).
IOP, intraocular pressure.

Serious Ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Serious ocular TEAEs, n (%)	7 (1.3)	28 (2.3)
Serious ocular TEAEs in ≥2 patients in any treatment group, n (%)		
Cataract[a]	1 (0.2)	7 (0.6)
Retinal detachment	1 (0.2)	6 (0.5)
Retinal hemorrhage	1 (0.2)	4 (0.3)
IOP increased	0	3 (0.2)
Vitreous hemorrhage	0	3 (0.2)
Retinal tear	0	2 (0.2)

[a]Includes cataract, cataract nuclear, and cataract subcapsular although these terms did not meet the 2-patient threshold.

Non-Ocular TEAEs, APTC Events and Deaths

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Any non-ocular TEAEs, n (%)	396 (71.2)	884 (72.6)
Any serious non-ocular TEAEs, n (%)	112 (20.1)	256 (21.0)
APTC events, n (%)[a]	23 (4.1)	45 (3.7)
Any death, n (%)[a]	17 (3.1)	33 (2.7)

[a]Treatment emergent.
APTC, Anti-Platelet Trialists' Collaboration.

Conclusions

- In this pooled analysis, the incidence of IOI was low and similar between aflibercept 8 mg and 2 mg
  - No cases of endophthalmitis were reported with aflibercept 8 mg, whereas 2 cases were reported with aflibercept 2 mg
  - No cases of occlusive retinal vasculitis were reported through Week 96 in any treatment group
- The incidence of non-ocular TEAEs, including serious TEAEs, APTC events, and deaths, was similar between aflibercept 8 mg and 2 mg
- Overall, aflibercept 8 mg demonstrated comparable safety to aflibercept 2 mg for up to 96 weeks across the CANDELA, PULSAR, and PHOTON trials