Pooled Safety Analysis of Aflibercept 8 mg in the CANDELA, PHOTON, and PULSAR Trials

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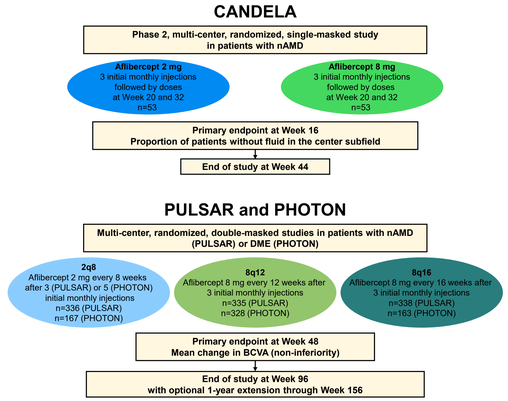
BACKGROUND & PURPOSE

- The high-dose formulation of aflibercept (8 mg) was developed to deliver a molar dose that is 4 times greater than that of aflibercept 2 mg, potentially suppressing vascular endothelial growth factor signaling over a longer duration of time
- In clinical trials of patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME), aflibercept 8 mg every 12 or 16 weeks (8q12 or 8q16) after 3 initial monthly injections demonstrated comparable safety to aflibercept 2 mg every 8 weeks (2q8) after 3 (nAMD) or 5 (DME) initial monthly injections
- The purpose of the current study was to evaluate the safety of aflibercept 8 mg in a large patient population by pooling safety data across clinical trials of aflibercept 8 mg

METHODS

- Safety data from 3 multi-center clinical trials comparing the efficacy and safety of aflibercept 8 mg versus 2 mg were pooled (**Figure 1**):
  - The phase 2 CANDELA trial and Phase 3 PULSAR trial in treatment-naïve patients with nAMD
  - The phase 2/3 PHOTON trial in treatment-naïve and previously treated patients with DME
- Data from the safety analysis set for aflibercept 8 mg and 2 mg were pooled through Week 44 of the CANDELA trial and through Week 48 of the ongoing 96-week PULSAR and PHOTON trials
- Ocular and non-ocular treatment-emergent adverse events (TEAEs) were summarized descriptively

Figure 1. Study Designs of Clinical Trials Evaluating Aflibercept 8 mg in Patients with nAMD and DME



BCVA, best-corrected visual acuity.

RESULTS

- Overall, safety data for 1773 patients (aflibercept 8 mg: n=1217; aflibercept 2 mg: n=556) were evaluated (**Table 1**)

Table 1. Patients Evaluated in the Pooled Safety Analysis

	Aflibercept 2 mg Pooled	8q12	8q16	Aflibercept 8 mg Pooled[a]
CANDELA, n	53	53[b]	0	53
PULSAR, n	336	335	338	673
PHOTON, n	167	328	163	491
Total, n	556	716	501	1217

[a]Aflibercept 8q12 and 8q16 combined.
[b]Patients in aflibercept 8 mg group received injections every 12 weeks through Week 32 after 3 initial monthly doses.

- Select baseline patient characteristics are shown in **Table 2**

Table 2. Baseline Demographics

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Age group, n (%)		
<65 years	141 (25.4)	349 (28.7)
≥65-<75 years	196 (35.3)	441 (36.2)
≥75 years	219 (39.4)	427 (35.1)
Female, n (%)	299 (53.8)	574 (47.2)
White, n (%)	412 (74.1)	927 (76.2)
Hispanic or Latino, n (%)	47 (8.5)	106 (8.7)

- The mean number of injections ranged from 5.0 to 6.9, and the mean treatment duration ranged from 45.5 to 46.5 weeks across treatment groups (**Table 3**)

Table 3. Aflibercept Exposure

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Number of injections, mean (SD)	6.9 (1.1)	5.5 (0.9)
Treatment duration, mean (SD), weeks	45.5 (7.4)	45.9 (7.5)

- The incidence of ocular TEAEs in the study eye was similar across treatment groups (**Tables 4–6**)
- No cases of endophthalmitis or occlusive retinal vasculitis or ischemic optic neuropathy were reported through Week 48

Table 4. Ocular TEAEs in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 ocular TEAE, n (%)	196 (35.3)	428 (35.2)
Ocular TEAEs occurring in ≥2% of patients in any treatment group, n (%)		
Cataract	12 (2.2)	37 (3.0)
Conjunctival hemorrhage	13 (2.3)	36 (3.0)
Intraocular pressure increased	15 (2.7)	36 (3.0)
Vitreous floaters	15 (2.7)	36 (3.0)
Reduced visual acuity	25 (4.5)	35 (2.9)
Vitreous detachment	9 (1.6)	33 (2.7)
Retinal hemorrhage	17 (3.1)	28 (2.3)
Punctuate keratitis	7 (1.3)	17 (1.4)
Subretinal fluid	12 (2.2)	16 (1.3)

Table 5. Intraocular Inflammation in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Intraocular inflammation, n (%)[a]	3 (0.5)	10 (0.8)

[a]Reported terms: chorioretinitis, iridocyclitis, iritis, uveitis, vitreal cells, and vitritis.

Table 6. Serious Ocular TEAEs in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 serious ocular TEAE, n (%)	4 (0.7)	16 (1.3)
Serious ocular TEAEs in ≥2 patients in any treatment group, n (%)		
Retinal detachment	0 (0)	5 (0.4)
Intraocular pressure increased	0 (0)	3 (0.2)
Retinal hemorrhage	1 (0.2)	2 (0.2)
Vitreous hemorrhage	0 (0)	2 (0.2)

- The incidences of non-ocular TEAEs, APTC events, and death were similar across treatment groups (**Tables 7 and 8**)

Table 7. Non-ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 non-ocular TEAE, n (%)	281 (50.5)	654 (53.7)
Non-ocular TEAEs occurring in ≥2% of patients in any treatment group, n (%)		
Hypertension	25 (4.5)	75 (6.2)
COVID-19	18 (3.2)	69 (5.7)
Nasopharyngitis	21 (3.8)	43 (3.5)
Back pain	17 (3.1)	34 (2.8)
Headache	10 (1.8)	28 (2.3)
Urinary tract infection	15 (2.7)	28 (2.3)
Atrial fibrillation	11 (2.0)	6 (0.5)
Any non-ocular serious TEAEs[a], n(%)	76 (13.7)	145 (11.9)

COVID-19, coronavirus disease 2019.
[a]No reported term occurred in >1% of patients.

Table 8. APTC Events and Death

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 APTC event, n (%)	11 (2.0)	18 (1.5)
Non-fatal stroke	2 (0.4)	9 (0.7)
Non-fatal myocardial infarction	5 (0.9)	5 (0.4)
Vascular death	4 (0.7)	4 (0.3)
Death, n (%)	9 (1.6)	14 (1.2)

APTC, Anti-Platelet Trialists' Collaboration.

Limitation

- This analysis was descriptive and is limited to the recently reported clinical trials evaluating aflibercept 8 mg in nAMD and DME

CONCLUSIONS

- In this pooled analysis, aflibercept 8 mg demonstrated similar safety to aflibercept 2 mg across the CANDELA, PHOTON, and PULSAR trials
- Incidences of IOI were low and similar between aflibercept 8 mg and 2 mg, with no reports of endophthalmitis, occlusive retinal vasculitis, or ischemic optic neuropathy
- There were no clinically significant increases in IOP reported with aflibercept 8mg
- Incidence of non ocular events, including SAEs, APTC events, and deaths, were similar between aflibercept 8 mg and 2 mg

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Poster presented by Eric Schneider, MD, email: eschneider@tnretina.com, at the ARVO 2023 Meeting, April 23-27, 2023