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

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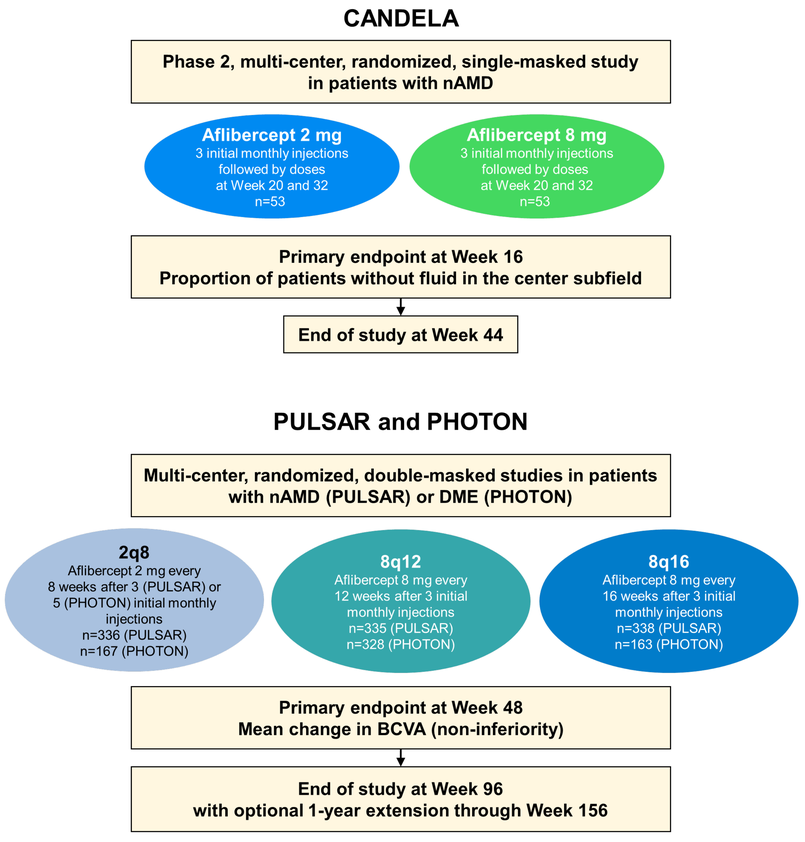
INTRODUCTION

- 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 pivotal clinical trials, aflibercept 8 mg demonstrated improved functional and anatomic outcomes at dosing intervals of ≥12 weeks in patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)
- These findings supported regulatory approval of aflibercept 8 mg for the treatment of nAMD, DME, and diabetic retinopathy (DR) in the US[1]
- 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 (NCT04126317) and phase 3 PULSAR (NCT04423718) trial in treatment-naive patients with nAMD
  - The phase 2/3 PHOTON (NCT04429503) 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 96-week PULSAR and PHOTON trials
  - Per original study protocol, treatment-emergent adverse events (TEAEs) reported by investigators were coded using the latest available version of Medical Dictionary for Regulatory Activities
  - Reported terms for the study eye were pooled for the purpose of this analysis, and data 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 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 the aflibercept 8 mg group received injections every 12 weeks through Week 32 after 3 initial monthly doses.

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 ischemic optic neuropathy, endophthalmitis, or occlusive retinal vasculitis 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 in ≥2% of patients in any treatment group, n (%)		
Cataract	12 (2.2)	37 (3.0)
Conjunctival hemorrhage	13 (2.3)	36 (3.0)
Vitreous floaters	15 (2.7)	36 (3.0)
Visual acuity reduced	25 (4.5)	35 (2.9)
Vitreous detachment	9 (1.6)	33 (2.7)
Intraocular pressure increased	13 (2.3)	28 (2.3)
Retinal hemorrhage	17 (3.1)	28 (2.3)
Subretinal fluid	12 (2.2)	16 (1.3)

Table 5. IOI in the Study Eye

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

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

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	5 (0.4)
Intraocular pressure increased	0	3 (0.2)
Retinal hemorrhage	1 (0.2)	2 (0.2)
Vitreous hemorrhage	0	2 (0.2)

- The incidences of non-ocular TEAEs, Anti-Platelet Trialists' Collaboration (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 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)
Patients with ≥1 non-ocular serious TEAEs, n (%)[a]	76 (13.7)	145 (11.9)

[a]No non-ocular serious TEAEs were reported in >1% of patients.
COVID-19, coronavirus disease 2019.

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)

Limitation

- This pooled analysis was limited to available safety data for aflibercept 8 mg from the following trials:
- CANDELA (phase 2): 44-week data from 106 patients with nAMD
- PULSAR (phase 3): 48-week data from 1009 patients with nAMD
- PHOTON (phase 2/3): 48-week data from 658 patients with 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 ischemic optic neuropathy, endophthalmitis, or occlusive retinal vasculitis
- There were no clinically significant increases in intraocular pressure reported with aflibercept 8 mg
- The incidence of non-ocular TEAEs, including serious TEAEs, APTC events, and deaths, was similar between aflibercept 8 mg and 2 mg

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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