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

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Disclosures

- Dr Ferrone has served as a consultant for Allergan, Apellis, Annexon, Zeiss, Ophthea, Regeneron, and Genentech; has received research support from Alexion, Alkeus, Apellis, EyePoint, Genentech, Gyroscope, Ophthea, Regeneron Pharmaceuticals, Inc., and RegenXBio; and has been a shareholder of ArcticDx
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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 of aflibercept 2 mg, potentially suppressing VEGF signaling over a longer duration of time

- Aflibercept 8 mg demonstrated comparable efficacy and safety versus aflibercept 2 mg in the proof-of concept phase 2 CANDELA trial and the pivotal phase 3 PULSAR trial in nAMD and the phase 2/3 PHOTON trial in DME[1-3]

- A pooled safety analysis was conducted in order to provide a robust evaluation of the overall safety profile of aflibercept 8 mg

This analysis evaluated the safety of aflibercept 8 mg and 2 mg across the CANDELA, PHOTON, and PULSAR trials

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

1. Brown DM. High dose aflibercept for neovascular AMD. Angiogenesis, Exudation, and Degeneration. Feb 11-12, 2022; Virtual. 2. Lanzetta P. Intravitreal aflibercept injection 8 mg for nAMD: results from the phase 3 PULSAR trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL. 3. Brown DM. Intravitreal aflibercept injection 8 mg for DME: results from the phase 2/3 PHOTON trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL.

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]3 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.

Methods

- 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, TEAEs reported by investigators were coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA)
  - Reported terms for the study eye were pooled for the purpose of this analysis, and data were summarized descriptively

TEAE, treatment-emergent adverse event.

Sample Size

	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 injections.

Baseline Demographics

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Female, n (%)	299 (53.8)	574 (47.2)
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)
White, n (%)	412 (74.1)	927 (76.2)
Hispanic or Latino, n (%)	47 (8.5)	106 (8.7)

Aflibercept Exposure

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Total number of injections	3864	6676
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)

Ocular TEAEs

	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)

- No cases of ischemic optic neuropathy were reported through Week 48

Intraocular Inflammation

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

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

- No cases of endophthalmitis or vasculitis were reported through Week 48

Serious Ocular TEAEs

	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)

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)

COVID-19, coronavirus disease 2019.

Serious Non-ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 non-ocular serious TEAE, n (%)	76 (13.7)	145 (11.9)
Serious non-ocular TEAEs in ≥4 patients in any treatment group, n (%)		
Pneumonia	2 (0.4)	8 (0.7)
Cerebrovascular accident	2 (0.4)	7 (0.6)
Myocardial infarction	3 (0.5)	5 (0.4)
Chest pain	1 (0.2)	5 (0.4)
COVID-19	1 (0.2)	5 (0.4)
Acute kidney injury	1 (0.2)	5 (0.4)
Acute respiratory failure	2 (0.4)	4 (0.3)
Acute left ventricular failure	4 (0.7)	3 (0.2)
Hyponatremia	4 (0.7)	2 (0.2)
Urinary tract infection	4 (0.7)	1 (<0.1)

APTC Events and Deaths

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with ≥1 APTC event,[a] 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,[a,b] n (%)	9 (1.6)	14 (1.2)

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

Limitations

- 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, incidences of intraocular inflammation were low and similar between aflibercept 8 mg and 2 mg, with no reports of endophthalmitis or vasculitis
- No cases of ischemic optic neuropathy were reported
- 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
- Overall, aflibercept 8 mg demonstrated similar safety to aflibercept 2 mg across the CANDELA, PULSAR, and PHOTON trials