Aflibercept 8 mg: Safety Outcomes From the CANDELA, PULSAR, and PHOTON Studies

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Disclosures

- Dr. Wells has served as a consultant and advisory board member for Genentech/Roche and as an investigator for 4DMT, Adverum, Aviceda, Coherus, Genentech, Iveric Bio, Neurotech, Opthea, and Regeneron Pharmaceuticals, Inc.
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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 of time
- 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 PULSAR trial in nAMD, and the pivotal PHOTON trial in DME[1-3]
  - Findings from these trials supported regulatory approval of aflibercept 8 mg for the treatment of nAMD, DME, and DR in the United States and nAMD and DME in the European Union[4,5]
- An analysis of pooled safety data from patients treated with aflibercept 8 mg or 2 mg through Week 44 of the CANDELA trial and through Week 48 of the PULSAR and PHOTON trials showed that the safety profile of aflibercept 8 mg was similar to that of aflibercept 2 mg
- The present analysis, including more than 1200 patients who received more than 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; DR, diabetic retinopathy; nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Brown DM. High dose aflibercept for neovascular AMD. Presented at: Angiogenesis, Exudation, and Degeneration; February 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. 4. EYLEA HD [prescribing information]. Regeneron Pharmaceuticals, Inc. August 2023. 5. EYLEA HD [summary of product characteristics]. Regeneron Pharmaceuticals, Inc. January 2024.

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.

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 96 of the PULSAR and PHOTON trials
  - TEAEs reported by investigators were coded using the latest available version of Medical Dictionary for Regulatory Activities (MedDRA)
  - Events were pooled across trials 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[b]	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 received injections every 12 weeks through Week 32.

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 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)

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]	51 (9.2)	133 (10.9)
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)
Intraocular inflammation, n (%)	9 (1.6)	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

IOI, intraocular inflammation.

IOP in the Study Eye

	CANDELA		PULSAR		PHOTON	
	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)	Aflibercept 2 mg (n=336)	Aflibercept 8 mg[a] (n=673)	Aflibercept 2 mg (n=167)	Aflibercept 8 mg[a] (n=491)
IOP increase from baseline ≥10 mmHg pre-injection at any visit, n (%)	0	2 (3.8)	11 (3.3)	18 (2.7)	5 (3.0)	28 (5.7)
IOP ≥35 mmHg pre- or post-injection at any visit, n (%)	0	0	2 (0.6)	4 (0.6)	2 (1.2)	2 (0.4)

[a]Data for the aflibercept 8q12 and 8q16 groups were pooled.
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)
Intraocular pressure 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

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Non-ocular TEAEs, n (%)	396 (71.2)	884 (72.6)
Non-ocular TEAEs in ≥3% of patients in any treatment group, n (%)		
COVID-19	77 (13.8)	203 (16.7)
Hypertension	41 (7.4)	114 (9.4)
Nasopharyngitis	39 (7.0)	75 (6.2)
Back pain	28 (5.0)	49 (4.0)
Urinary tract infection	31 (5.6)	45 (3.7)
Arthralgia	13 (2.3)	40 (3.3)
Fall	18 (3.2)	23 (1.9)

COVID-19, coronavirus disease 2019.

Potentially Clinically Significant Blood Pressure Values

	CANDELA		PULSAR		PHOTON	
	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)	Aflibercept 2 mg (n=335)[a]	Aflibercept 8 mg (n=671)[a,b]	Aflibercept 2 mg (n=165)[c]	Aflibercept 8 mg (n=489)[b,c]
Systolic BP ≥160 mmHg and increase from baseline ≥20 mmHg, n (%)	9 (17.0)	6 (11.3)	41 (12.2)	87 (13.0)	51 (30.9)	154 (31.5)
Diastolic BP ≥110 mmHg and increase from baseline ≥10 mmHg, n (%)	1 (1.9)	0	4 (1.2)	3 (0.4)	4 (2.4)	18 (3.7)

[a]Patients at baseline without an abnormal blood pressure assessment and ≥1 valid blood pressure value after treatment initiation. Patients with missing or abnormal values at baseline were excluded.
[b]Data for the aflibercept 8q12 and 8q16 groups were pooled.
[c]Patients with a valid post-baseline blood pressure value.
BP, blood pressure.

Immunogenicity to Aflibercept Through Year 1

	VIEW 1/VIEW 2 (nAMD)		VISTA/VIVID (DME)
	Control[a] (n=595)	Aflibercept 0.5 mg and 2 mg (n=1817)	Aflibercept 2 mg (n=578)
Patients with ADA, (%)			
Pre-treatment ADA	1.0-1.6	1.8-1.9	0.7-4.5
Treatment-emergent ADA	1.7-3.3	1.5-1.9	0.7-1.9

Rates of ADA induction to aflibercept in the ranibizumab control group of the VIEW 1/VIEW 2 trials were comparable to those observed in the aflibercept-treated groups

	PULSAR (nAMD)		PHOTON (DME)	
	Aflibercept 2 mg (n=260)	Aflibercept 8 mg (n=523)	Aflibercept 2 mg (n=137)	Aflibercept 8 mg (n=404)
Patients with ADA,[b] (%)				
Pre-treatment ADA	2.7	2.1	2.2	3.0
Treatment-emergent ADA	1.5	3.8	0	1.2

Proportions of patients developing ADA were low and similar pre- and post-aflibercept treatment across trials, demonstrating little to no ADA induction following aflibercept treatment

[a]Immunoreactivity in aflibercept ADA assay for the ranibizumab 0.5-mg control group. Patients were treatment naïve at baseline and received no aflibercept treatment in either eye.
[b]ADA assay was revalidated according to the 2019 FDA Guidance.[1] ADA methods target a ~1% false positive rate.
ADA, anti-drug antibodies.
1. US Food and Drug Administration. Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products–Developing and Validating Assays for Anti-Drug Antibody Detection. 2019. Accessed January 16, 2024.

Serious Non-ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Serious non-ocular TEAEs, n (%)	112 (20.1)	256 (21.0)
Serious non-ocular TEAEs in ≥6 patients in any treatment group, n (%)		
Pneumonia	3 (0.5)	16 (1.3)
Acute myocardial infarction	4 (0.7)	13 (1.1)
Myocardial infarction	4 (0.7)	12 (1.0)
Osteoarthritis	3 (0.5)	10 (0.8)
Acute kidney injury	3 (0.5)	9 (0.7)
Cerebrovascular accident	2 (0.4)	9 (0.7)
Coronary artery disease	2 (0.4)	8 (0.7)
Chest pain	1 (0.2)	7 (0.6)
COVID-19	1 (0.2)	7 (0.6)
Acute respiratory failure	2 (0.4)	6 (0.5)
Pulmonary embolism	1 (0.2)	6 (0.5)

APTC Events and Deaths

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
APTC events,[a] n (%)	23 (4.1)	45 (3.7)
Non-fatal myocardial infarction	9 (1.6)	18 (1.5)
Vascular death	10 (1.8)	14 (1.2)
Non-fatal stroke	4 (0.7)	13 (1.1)
Any death,[a] n (%)	17 (3.1)	33 (2.7)

[a]Treatment emergent.
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):** 96-week data from 1009 patients with nAMD
  - **PHOTON (phase 2/3):** 96-week data from 658 patients with DME

Conclusions

- In this pooled analysis, the incidence of intraocular inflammation was low and similar between aflibercept 8 mg and 2 mg
  - No cases of endophthalmitis were reported with aflibercept 8 mg, whereas 2 cases of endophthalmitis were reported with aflibercept 2 mg
- 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
- 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