Pooled Safety Analysis of the CANDELA, PHOTON, and PULSAR Trials Up to 96 Weeks Demonstrates Comparable Safety Profiles with Aflibercept 8 mg and 2 mg

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Presented at the 24th European Society of Retina Specialists (EURETINA) Congress, Barcelona, Spain, September 19–22, 2024

Disclosures

- **AS** has served as a consultant for Allergan, Apellis, Bayer, Novartis, and Roche
  - **ES** is a consultant for Carl Zeiss Meditec, Inc., Notal Vision, and Iveric Bio. **USO**, **CT**, and **ASc** are employees of Bayer AG. **AJB**, **KWC**, **RV**, **KR**, and **RR** are employees and stockholders of Regeneron Pharmaceuticals, Inc. **XZ**, **PMW**, and **SL** are employees of Bayer Consumer Care AG
- The CANDELA and PHOTON studies were sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY), and the PULSAR study was funded by Bayer AG (Leverkusen, Germany). The sponsor participated in the design and conduct of the studies, analysis of the data, and preparation of this presentation
- Study disclosures: These studies include research conducted on human patients; Institutional Review Board approval was obtained prior to study initiation
- The pooled safety analysis of intravitreal aflibercept 8 mg from CANDELA, PHOTON, and PULSAR was previously presented at the ARVO Annual Meeting, May 5–9, 2024, Seattle, WA, USA
- Medical writing support, under direction of the authors, was provided by ApotheCom and funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med* 2022;175:1298–1304)

Background and Methods

- The purpose of the current analysis was to evaluate the safety of aflibercept 8 mg and 2 mg up to 96 weeks
- Data from 3 multicenter, randomized clinical trials comparing the efficacy and safety of aflibercept 8 mg versus aflibercept 2 mg were pooled:
  - Phase 2 **CANDELA trial** in treatment-naïve patients with nAMD
  - Phase 3 **PULSAR trial** in treatment-naïve patients with nAMD
  - Phase 2/3 **PHOTON trial** in treatment-naïve and previously treated patients with DME
- Data were pooled through Week 44 of the CANDELA trial and through Week 96 of the PULSAR and PHOTON trials

Overall, safety data for **1773 patients were evaluated**

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

[a]Three initial monthly injections followed by injections at Weeks 20 and 32.
8q12, aflibercept 8 mg every 12 weeks; **8q16**, aflibercept 8 mg every 16 weeks; **DME**, diabetic macular edema; **nAMD**, neovascular age-related macular degeneration.

Baseline Demographics and Aflibercept Exposure in the Pooled Safety Analysis

		Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled[a] (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			
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)

SAF. [a]Aflibercept 8q12 and 8q16 combined.
SAF, safety analysis set; **SD**, standard deviation.

Ocular TEAEs in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with **≥1 ocular TEAE**, n (%)	263 (47.3)	583 (47.9)
Ocular TEAEs occurring 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)
Retinal hemorrhage	22 (4.0)	44 (3.6)

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

SAF. [a]Includes cataract, cataract cortical, cataract nuclear, cataract operation, cataract subcapsular, lenticular opacities, and posterior capsule opacifications, although not all terms met the ≥3% threshold.
TEAE, treatment-emergent adverse event.

IOI and IOP Increase Events in the Study Eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with **≥1 event of IOI**, 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
IOP, n (%)		
IOP increase from baseline ≥10 mmHg pre-injection[a]	16 (2.9)[b]	48 (3.9)[c]
IOP ≥35 mmHg pre- or post-injection[a]	4 (0.7)[d]	6 (0.5)[e]

SAF. [a]At any visit. [b]CANDELA (n=0), PULSAR (n=11), and PHOTON (n=5). [c]CANDELA (n=2), PULSAR (n=18), and 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).
IOI, intraocular inflammation; **IOP**, intraocular pressure.

Non-ocular TEAEs, APTC Events and Deaths

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with **≥1 non-ocular TEAE**, n (%)	396 (71.2)	884 (72.6)
Non-ocular TEAEs occurring in ≥5% of patients in any treatment group, n (%)	77 (13.8)	203 (16.7)
COVID-19	41 (7.4)	114 (9.4)
Hypertension	39 (7.0)	75 (6.2)
Nasopharyngitis	28 (5.0)	49 (4.0)
Back pain	31 (5.6)	45 (3.7)
Urinary tract infection	112 (20.1)	256 (21.0)
Patients with **≥1 APTC event**[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)
Deaths[a], n (%)	17 (3.1)	33 (2.7)

SAF. [a]Treatment-emergent.
APTC, Anti-Platelet Trialists' Collaboration; **COVID-19**, coronavirus disease 2019.

Serious Ocular and Serious Non-ocular TEAEs

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Patients with **≥1 serious ocular TEAE in the study eye**, n (%)	7 (1.3)	28 (2.3)
Serious ocular TEAEs in the study eye 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)
Patients with **≥1 serious non-ocular TEAE**, n (%)	112 (20.1)	256 (21.0)
Serious non-ocular TEAEs occurring in ≥1% of patients in any group, n (%)		
Pneumonia	3 (0.5)	16 (1.3)
Acute myocardial infarction	4 (0.7)	13 (1.1)

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

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[b]	1.0–1.6	1.8–1.9	0.4–2.9
Treatment-emergent ADA[c]	1.7–3.3	1.5–1.9	0.4–1.3

	PULSAR (nAMD)		PHOTON (DME)	
	Aflibercept 2 mg (n=260)	Aflibercept 8 mg (n=533)	Aflibercept 2 mg (n=137)	Aflibercept 8 mg (n=404)
Patients with ADA, %[d]				
Pre-treatment ADA[b]	2.7	2.1	2.2	3.0
Treatment-emergent ADA[c]	1.5	3.8	0	1.2

SAF. [a]Immunoreactivity in aflibercept ADA assay for ranibizumab 0.5 mg control group. Patients were treatment-naïve at baseline and received no aflibercept treatment in either eye. [b]Positive ADA result at baseline and titers in post-baseline samples <4-fold the baseline ADA titer value. [c]Negative or missing ADA result at baseline with at least one positive ADA result in post-baseline samples (VIEW 1/2, VISTA/VIVID, PULSAR, and PHOTON) OR positive ADA result at baseline with at least one post-baseline ADA titer result ≥4-fold the baseline titer value (VIEW 1/2 and VISTA/VIVID). [d]ADA assay was revalidated according to the 2019 FDA guidance.[6] ADA methods target a ~1% false positive rate. **ADA**, anti-drug antibodies. **FDA**, Food and Drug Administration. 6. US Food and Drug Administration. Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products–Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019). Available at: https://www.fda.gov/media/119788/download.

Conclusions

- 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 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 2 mg for up to 96 weeks across the CANDELA, PULSAR, and PHOTON trials