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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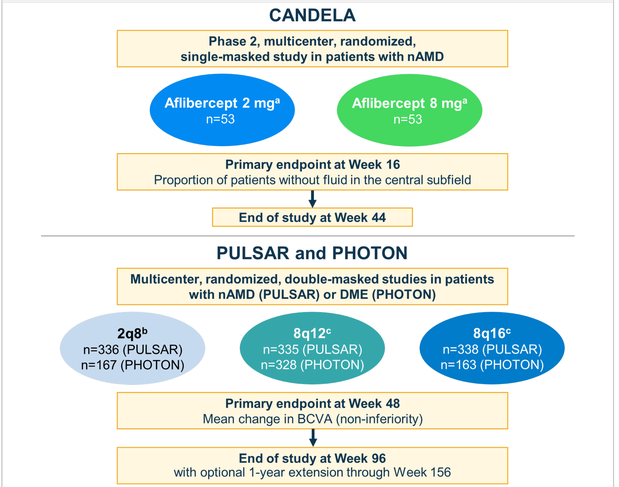
PURPOSE

Aflibercept 8 mg is a novel formulation that delivers a 4-fold higher molar dose than aflibercept 2 mg, potentially suppressing vascular endothelial growth factor 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 neovascular age-related macular degeneration (nAMD), the pivotal PULSAR trial in nAMD, and the pivotal PHOTON trial in diabetic macular edema (DME).[1–3] Findings from these trials supported regulatory approval of aflibercept 8 mg in the United States and European Union.[4–5] The present analysis, including more than 1200 patients, evaluated the safety of aflibercept 8 mg and 2 mg for up to 96 weeks across the CANDELA, PULSAR, and PHOTON trials.

METHODS

CANDELA was a single-masked, open-label, 44-week, phase 2 trial: treatment-naïve patients with nAMD were randomized 1:1 to receive 3 monthly injections of aflibercept 8 mg or 2 mg followed by injections at Weeks 20 and 32. PULSAR was a double-masked, 96-week, non-inferiority, phase 3 trial: patients with nAMD were randomized 1:1:1 to receive aflibercept 2 mg every 8 weeks (2q8), or 8 mg every 12 (8q12) or 16 weeks (8q16) after 3 initial monthly injections. PHOTON was a double-masked, 96-week, non-inferiority, phase 2/3 trial: patients with DME were randomized 1:2:1 to 2q8 after 5 monthly doses or 8q12 or 8q16 after 3 monthly doses (**Figure 1**). Safety data were pooled through Week 44 (CANDELA) and through Week 96 (PULSAR and PHOTON). Treatment-emergent adverse events (TEAEs) reported by investigators were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Data were summarized descriptively.

FIGURE 1:
CANDELA, PULSAR, and PHOTON study designs



[a]Three initial monthly injections followed by injections at Weeks 20 and 32. [b]After 3 (PULSAR) or 5 (PHOTON) initial monthly injections. [c]After 3 initial monthly injections. 2q8, aflibercept 2 mg every 8 weeks; 8q12, aflibercept 8 mg every 12 weeks; 8q16, aflibercept 8 mg every 16 weeks; BCVA, best-corrected visual acuity; DME, diabetic macular edema; nAMD, age-related macular degeneration.

RESULTS

Overall, 1773 patients (aflibercept 2 mg: n=556; aflibercept 8 mg: n=1217) were evaluated. Baseline characteristics were well-balanced between the pooled groups. The mean number of injections ranged from 8.3 (8 mg) to 11.6 (2 mg) (**Table 1**). Safety outcomes for aflibercept 2 mg and 8 mg were similar through Week 96 (**Tables 2–4**). 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. There were no cases of occlusive retinal vasculitis reported in the trials. Most cases of intraocular inflammation (IOI) were non-serious and mild or moderate in severity (**Table 2**). Proportions of patients developing anti-drug antibodies (ADA) were low and similar pre- and post-aflibercept treatment across trials, demonstrating little to no ADA induction following aflibercept treatment (**Table 5**).

TABLE 1:
Baseline demographics and aflibercept exposure

	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		
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. SAF, safety analysis set; SD, standard deviation.

TABLE 2:
Ocular TEAEs in the study eye through Week 96

n (%)	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Any ocular TEAE	263 (47.3)	583 (47.9)
Any ocular TEAE ≥4% in any group		
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)
Any serious ocular TEAE	7 (1.3)	28 (2.3)
Any serious ocular TEAE in ≥2 patients in any group		
Cataract[b]	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)
Any intraocular inflammation	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

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. [b]Includes cataract, cataract nuclear, and cataract subcapsular although these terms did not meet the 2-patient threshold. IOI, intraocular inflammation; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

TABLE 3:
IOP in the study eye through Week 96

n (%)	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
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). IOP, intraocular pressure; SAF, safety analysis set.

TABLE 4:
Non-ocular TEAEs, APTC events, and deaths through Week 96

n (%)	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)
Any non-ocular TEAE	396 (71.2)	884 (72.6)
Any non-ocular TEAE ≥5% in any group		
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)
Any serious non-ocular TEAE	112 (20.1)	256 (21.0)
Any serious non-ocular TEAE in ≥1% in any group		
Pneumonia	3 (0.5)	16 (1.3)
Acute myocardial infarction	4 (0.7)	13 (1.1)
APTC events[a]	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]	17 (3.1)	33 (2.7)

SAF. [a]Treatment-emergent. APTC, Anti-Platelet Trialists' Collaboration; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

TABLE 5:
Immunogenicity to aflibercept through Year 1

	VIEW 1/VIEW 2 (nAMD)		VISTA/VIVID (DME)
Patients with ADA, %	Control[a] (n=595)	Aflibercept 0.5 mg and 2 mg (n=1817)	Aflibercept 2 mg (n=578)
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)	
Patients with ADA, %[d]	Aflibercept 2 mg (n=260)	Aflibercept 8 mg (n=533)	Aflibercept 2 mg (n=137)	Aflibercept 8 mg (n=404)
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 less than 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 (VIEW1/2, 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 (VIEW1/2 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; DME, diabetic macular edema; nAMD, age-related macular degeneration; SAF, safety analysis set.

CONCLUSIONS

In this pooled analysis, aflibercept 8 mg demonstrated comparable safety to 2 mg for up to 96 weeks across the CANDELA, PULSAR, and PHOTON trials.

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.

Low immunogenicity in PULSAR and PHOTON was consistent with data from pivotal Phase 3 trials.

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Disclosures

ASt: Consultant for Allergan, Apellis, Bayer, Novartis, and Roche; **ES**: Consultant for Carl Zeiss Meditec, Inc., Notal Vision, and Iveric Bio; **USO**, **CT**, and **ASh**: Employees of Bayer AG; **AJB**, **KWC**, **RV**, **KR**, and **RR**: Employees and stockholders of Regeneron Pharmaceuticals, Inc.; **XZ**, **PMW**, and **SL**: Employees of Bayer Consumer Care AG.

Acknowledgments

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 study, analysis of the data, and preparation of this poster. Medical writing support, under the direction of the authors, was provided by ApotheCom and funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP) standards (*Ann Intern Med* 2022;175:1298–1304).

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Presented at The Association for Research in Vision and Ophthalmology (ARVO) 2024 Annual Meeting, Seattle, WA, USA, May 5–9, 2024