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A pooled analysis of the PULSAR and PHOTON trials through 96 weeks: Minimal impact of aflibercept 8 mg and 2 mg on intraocular pressure changes

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Purpose

- Acute increases in intraocular pressure (IOP) immediately following intravitreal injections of anti-vascular endothelial growth factor therapies[1] are common and have been associated with a range of factors including needle gauge, drug properties, injection speed and volume.[2-5] Most cases of increased IOP resolve without intervention[6]
- High-dose aflibercept 8 mg with extended dosing has demonstrated visual and anatomic benefits in patients with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) from the PULSAR and PHOTON trials[7,8]
- This analysis evaluated IOP increase and glaucoma-related outcomes in eyes receiving aflibercept 8 mg (70 µl) and 2 mg (50 µl) in the PULSAR (NCT04423718) and PHOTON (NCT04429503) trials through 96 weeks

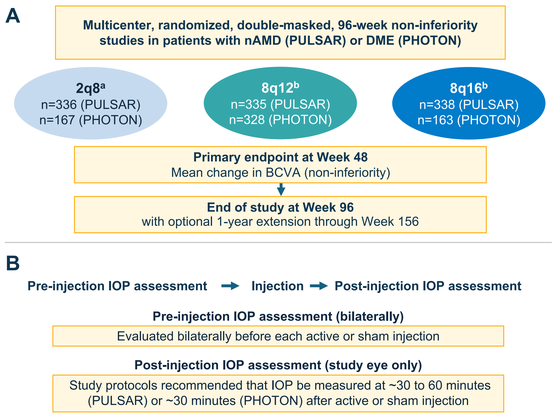
Conclusions

- This post hoc analysis of pooled safety data through Week 96 from the PULSAR and PHOTON trials found **IOP outcomes were comparable** between aflibercept 8 mg and aflibercept 2 mg, with **no long-term IOP or glaucoma-related TEAEs**
- The incidence of IOP increase and glaucoma-related TEAEs was **low in both treatment groups**
- Few patients **(≤0.8%) had pre- or post-injection IOP ≥35 mmHg** at any visit with aflibercept 8 mg and aflibercept 2 mg
- The rates of **anterior chamber paracentesis procedures were low** and performed following **<0.1% of injections administered** in the aflibercept 8 mg group
- **No clinically relevant difference in LS mean changes from pre- to post-injection IOP** of aflibercept 8 mg vs aflibercept 2 mg (0.83 [95% CI 0.67, 0.99] mmHg) was observed
- This analysis helps to further demonstrate the **consistent safety profile** of aflibercept 8 mg vs aflibercept 2 mg, which is also supported by a recent study of early IOP dynamics[9]

Methods

- In the Phase 3 PULSAR trial, patients with nAMD were randomized 1:1:1 to receive aflibercept 2 mg every 8 weeks (2q8), or aflibercept 8 mg every 12 (8q12) or 16 (8q16) weeks after 3 initial monthly injections (**Figure 1**)
- In the Phase 2/3 PHOTON trial, patients with DME were randomized 1:2:1 to receive aflibercept 2q8 after 5 initial monthly injections or aflibercept 8q12 or 8q16 after 3 initial monthly injections (**Figure 1**)
- Patients with uncontrolled glaucoma in the study eye (defined as IOP >25 mmHg despite treatment with anti-glaucoma medication [PULSAR] or ≥25 mmHg [PHOTON]) were ineligible
- The incidences of IOP increase or glaucoma-related treatment-emergent adverse events (TEAEs) from the PULSAR and PHOTON safety analysis sets were pooled through Week 96 and evaluated; for this analysis, data for the aflibercept 8q12 and 8q16 groups were combined

Figure 1: (A) Study design and (B) IOP assessment in PULSAR and PHOTON



The same method of measurement was used in each patient throughout the study (e.g., Goldmann applanation tonometry, rebound tonometry Icare, or Tono-pen™). On days when study drug was administered, sites were permitted to follow their usual post-injection monitoring routine. Reported IOP was the last reading recorded before the patient was permitted to leave the study site. [a]After 3 (PULSAR) or 5 (PHOTON) initial monthly injections. [b]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; IOP, intraocular pressure; nAMD, neovascular age-related macular degeneration.

Results

- Overall, 1667 patients were included in the safety analysis set. Baseline characteristics were balanced between treatment groups (**Table 1**)
- At baseline, mean (standard deviation [SD]) IOP was comparable for the aflibercept 2 mg (15.1 [3.0] mmHg) and aflibercept 8 mg (15.0 [3.2] mmHg) groups
- The proportion of patients with glaucoma-related medical history in the study eye was comparable across aflibercept treatment groups (aflibercept 2 mg: 8.2%; aflibercept 8 mg: 7.6% of patients)
- At Week 96, mean pre-injection IOP values were similar across treatment groups, with no sustained increase in IOP observed or trend toward increased IOP over time (**Figure 2**)

Results

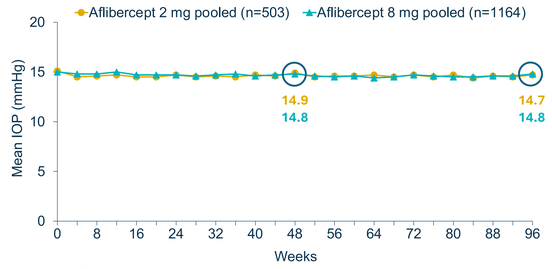
- The least squares (LS) mean change from pre- to post-injection IOP was comparable for patients in the pooled 2 mg and 8 mg groups with a difference of 0.83 (95% CI 0.67, 0.99) mmHg for 8 mg vs 2 mg (**Figure 3**)
- Through Week 96, the proportion of patients with a pre- or post-injection IOP ≥35 mmHg was low (≤0.8%) and comparable across the treatment groups (**Table 2**)
- The rate of anterior chamber paracentesis procedures performed through Week 96 was comparable across the treatment groups (aflibercept 2 mg, 0 procedures; aflibercept 8 mg, 5 [0.4%] procedures) and performed in 9/9762 (<0.1%) of injections administered in the aflibercept 8 mg group
- Rates of IOP- or glaucoma-related TEAEs were low and comparable across groups through Week 96 (**Table 3**)

Table 1: Baseline demographics, disease characteristics, and aflibercept exposure

	Aflibercept 2 mg pooled (n=503)	Aflibercept 8 mg pooled (n=1164)
Baseline demographics		
Female, n (%)	263 (52.3)	544 (46.7)
Age group, n (%)		
<65 years	137 (27.2)	346 (29.7)
≥65– <75 years	180 (35.8)	425 (36.5)
≥75 years	186 (37.0)	393 (33.8)
White, n (%)	361 (71.8)	875 (75.2)
Hispanic or Latino, n (%)	43 (8.5)	104 (8.9)
Baseline disease characteristics		
Mean (SD) IOP, mmHg	15.1 (3.0)	15.0 (3.2)
Medical history of IOP increase/glaucoma, n (%)	41 (8.2)	88 (7.6)
Aflibercept exposure		
Total number of injections	6159	9762

Safety analysis set. Data are in the study eye. IOP, intraocular pressure; SD, standard deviation.

Figure 2: Mean pre-injection IOP through Week 96



Safety analysis set. IOP, intraocular pressure.

Acknowledgments

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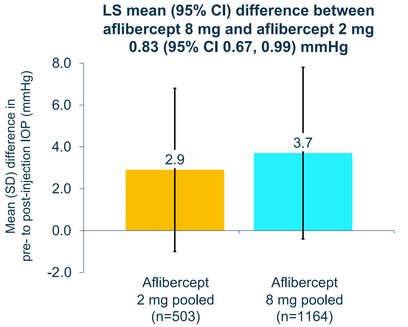
Figure 3: Differences in pre- to post-injection IOP in study eyes through Week 96



Safety analysis set through Week 96. Active dosing visits. CI, confidence interval; IOP, intraocular pressure; LS, least squares; SD, standard deviation.

Table 2: IOP ≥35 mmHg through Week 96 in the study eye

	Aflibercept 2 mg pooled (n=503)	Aflibercept 8 mg pooled (n=1164)
Pre- or post-injection IOP ≥35 mmHg, n (%)	4 (0.8)	6 (0.5)
Pre-injection IOP ≥35 mmHg, n (%)	1 (0.2)	2 (0.2)
Post-injection IOP ≥35 mmHg, n (%)	3 (0.6)	4 (0.3)

Safety analysis set. IOP, intraocular pressure.

Table 3: IOP- and glaucoma-related TEAEs in the study eye through Week 96

	Aflibercept 2 mg pooled (n=503)	Aflibercept 8 mg pooled (n=1164)
Patients with ≥1 TEAE, n (%)	22 (4.4)	53 (4.6)
Angle closure glaucoma	1 (0.2)	2 (0.2)
Borderline glaucoma	0	2 (0.2)
Glaucoma	1 (0.2)	6 (0.5)
Intraocular pressure increased	17 (3.4)	34 (2.9)
Ocular hypertension	3 (0.6)	12 (1.0)
Open angle glaucoma	1 (0.2)	1 (<0.1)

Safety analysis set. IOP, intraocular pressure; TEAE, treatment-emergent adverse event.

Disclosures

Sergio Leal: Employee investor and patent holder Bayer Consumer Care AG.

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