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A pooled analysis of the CANDELA, PHOTON, and PULSAR trials through 96 weeks: Comparably low intraocular inflammation-related events with aflibercept 8 mg and 2 mg

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Purpose

- Anti-vascular endothelial growth factor (VEGF) agents are the standard of care for the management of neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME)[1]
- Intraocular inflammation (IOI) is a well-known, yet rare, adverse event associated with any intraocular procedure, such as the intravitreal injection of anti-VEGF agents[2,3]
- The aim of this analysis was to evaluate the safety of aflibercept 8 mg, with a focus on treatment-emergent adverse events (TEAEs) associated with IOI over 96 weeks in a large patient population, by pooling safety data across the CANDELA, PULSAR, and PHOTON clinical trials

Conclusions

- In this pooled analysis, the incidence of IOI-related events with aflibercept 8 mg was **low and comparable** to that for aflibercept 2 mg through 96 weeks across the CANDELA, PHOTON, and PULSAR trials
- **Most IOI-related events were mild in severity** for both aflibercept 8 mg and aflibercept 2 mg, with 1 case of a severe IOI-related event reported with aflibercept 2 mg
- **No cases of endophthalmitis were reported** with aflibercept 8 mg, and 2 cases were reported with aflibercept 2 mg
- **Most patients** receiving aflibercept 8 mg and aflibercept 2 mg who developed IOI-related events **had recovered or were recovering** at the completion of the trials
- The findings from this pooled analysis of IOI-related safety data across the CANDELA, PULSAR, and PHOTON trials **further support the safety profile of aflibercept 8 mg**

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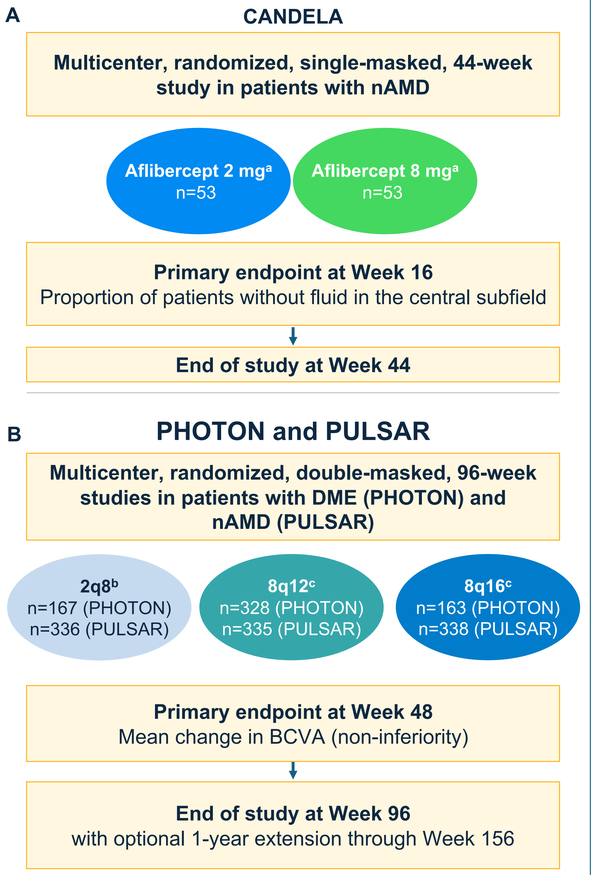
Methods

- In the Phase 2 CANDELA trial, patients with treatment-naïve nAMD were randomized 1:1 to receive 3 monthly doses of aflibercept 8 mg or aflibercept 2 mg followed by doses at Week 20 and Week 32 (**Figure 1A**)
- In the Phase 2/3 PHOTON trial, patients with DME were randomized 1:2:1 to receive aflibercept 2 mg every 8 weeks (2q8) following 5 initial monthly injections, or aflibercept 8 mg every 12 weeks (8q12) or 16 weeks (8q16) after 3 initial monthly injections (**Figure 1B**)
- In the Phase 3 PULSAR trial, patients with treatment-naïve nAMD were randomly assigned 1:1:1 to receive aflibercept 2q8, 8q12, or 8q16 following 3 initial monthly injections (**Figure 1B**)
- Data for IOI-related events from the safety analysis set were pooled through Week 44 from the CANDELA trial and through Week 96 from the PHOTON and PULSAR trials

Figure 1: Study design of the (A) CANDELA and the pivotal (B) PHOTON and PULSAR trials



[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, neovascular age-related macular degeneration.

Results

- Overall, 1773 patients were treated and evaluated. Baseline demographics were generally similar, and mean aflibercept treatment duration was comparable between the pooled treatment groups (**Table 1**)
- One or more IOI-related events were reported in 1.6% (n=9) of patients receiving aflibercept 2 mg and 1.3% (n=16) of patients receiving aflibercept 8 mg, respectively (**Table 2**)
- Two cases of endophthalmitis were reported with aflibercept 2 mg, and none occurred with aflibercept 8 mg. One event was mild, non-serious and study drug-related, while the second event was considered severe, serious, and related to the injection procedure, but not drug-related
- Most IOI-related events were mild, and a small number were moderate or severe (**Table 2**)
- One case of retinal vasculitis occurred with aflibercept 2 mg, and none occurred with aflibercept 8 mg
- Of the patients who developed IOI-related events with aflibercept 2 mg and aflibercept 8 mg, most had recovered or were recovering at the time of analysis (**Table 3**)
- Aflibercept treatment was withdrawn for 3 patients following IOI-related events (**Table 3**)
- Visual outcomes were comparable between the treatment groups for patients with IOI-related events, with mean (standard deviation [SD]) BCVA changes from baseline to Week 96 of +0.3 (12.3) and +0.9 (14.3) letter improvements for the aflibercept 2 mg and aflibercept 8 mg groups, respectively

Table 1: Baseline demographics and aflibercept exposure

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled[a] (n=1217)
Baseline demographics		
Female, n (%)	299 (53.8)	574 (47.2)
Age, 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)

Safety analysis set. [a]Aflibercept 8q12 and 8q16 combined. 8q12, aflibercept 8 mg every 12 weeks; 8q16, aflibercept 8 mg every 16 weeks; SD, standard deviation.

References
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Table 2: IOI-related events in the study eye

n (%)	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled[a] (n=1217)
Patients with ≥1 IOI-related event	**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)[b]
Endophthalmitis	2 (0.4)	0
Eye inflammation	1 (0.2)	0
Hypopyon	1 (0.2)	0
Severity of IOI-related events		
Mild	7 (1.3)	12 (1.0)
Moderate	1 (0.2)	4 (0.3)
Severe	1 (0.2)[c]	0

Safety analysis set. [a]Aflibercept 8q12 and 8q16 combined. [b]The event was considered mild and neither treatment nor procedure related; the dose and treatment were not changed, no remedial therapy was documented, and the patient had not recovered at the time of the analysis. [c]The patient experienced endophthalmitis; the event was considered related to the injection procedure but not treatment related. Therapy was interrupted, remedial therapies were provided, and the patient recovered. 8q12, aflibercept 8 mg every 12 weeks; 8q16, aflibercept 8 mg every 16 weeks; IOI, intraocular inflammation.

Table 3: Treatment status of patients with IOI-related events in the study eye

	Aflibercept 2 mg pooled (n=556)	Aflibercept 8 mg pooled (n=1217)[a]
Patients recovered/recovering from IOI-related event, n/# of IOI-related events (%)	7/9 (77.8)	11/16 (69.0)
Treatment status after IOI-related event, n/# of IOI-related events (%)		
No change	4/9 (44.4)	12/16 (75.0)[b]
Treatment interrupted	4/9 (44.4)	1/16 (6.3)
Treatment withdrawn	1/9 (11.1)[c]	2/16 (12.5)[d]
Treatment plan/study ended	0/9 (0)	1/16 (6.3)

Safety analysis set. [a]Aflibercept 8q12 and 8q16 combined. [b]Three patients who continued treatment developed the same IOI-related event twice (all events were non-serious, mild, and resolved): vitreal cells and eye inflammation (n=1 each) in the aflibercept 2 mg group and iritis (n=1) in the aflibercept 8 mg group. [c]The patient developed a moderate case of uveitis, received remedial therapy, and their recovery status was not available at the time of the analysis. [d]One patient developed a moderate case of iridocyclitis, received remedial treatment, and had not recovered at the time of the analysis; one patient developed a moderate case of iritis, received remedial treatment, and had recovered at the time of the analysis. 8q12, aflibercept 8 mg every 12 weeks; 8q16, aflibercept 8 mg every 16 weeks; IOI, intraocular inflammation.

Disclosures

Justus G. Garweg: Consultant/speaker for AbbVie, Bayer, Novartis, and Roche; research funding from Bayer, Novartis, and Roche. **Andreas Stahl (presenting co-author):** Consultant for Allergan, Apellis, Bayer, Novartis, and Roche.

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