Population Pharmacokinetic Modeling and Simulation of Ocular Clearance for Aflibercept 8 mg and 2 mg and Association With Durability of Effect

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Disclosures

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- Trials include research conducted on human patients. Institutional Review Board approval was obtained prior to initiation of each trial
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Objective and Methods

Objective: To evaluate pharmacokinetic and patient-specific characteristics that affect dosing interval duration for aflibercept 8 mg

Methods

PopPK Modeling and Simulation

PopPK model development:

- A semi-mechanistic PopPK model developed using data for free and adjusted bound aflibercept concentrations in plasma for **2744 individuals** from **16 clinical trials** evaluating:
  - Intravenous aflibercept 0.3 mg/kg to 4 mg/kg
  - Subcutaneous aflibercept 0.025 mg/kg to 2 mg/kg
  - Intravitreal aflibercept 0.05 mg to 8 mg

Simulation:

- **Virtual patient population: 10,000 patients with nAMD or DME** (5000 patients each)[a]
- Free aflibercept concentrations were simulated over time in the ocular compartment for the intravitreal aflibercept 8-mg and 2-mg drug products

Exposure-response Modeling

- Two distinct exposure-response models were developed to assess the characteristics of aflibercept 8 mg–treated patients that may affect dosing interval shortening or extension
- Models were developed using:
  - Longitudinal dosing interval data and covariate information from aflibercept 8-mg clinical trials
    - Time to first dosing interval shortening model:

      726 patients with nAMD (CANDELA and PULSAR) and **491 patients with DME** (PHOTON)
    - Time to first dosing interval extension model:

      621 patients with nAMD (PULSAR) and **441 patients with DME** (PHOTON)
  - Post hoc Bayesian PopPK estimates of ocular clearance from each patient

[a]Patient characteristics randomly sampled from the analysis population and variability around the estimate of ocular clearance.
DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; PopPK, population pharmacokinetic.

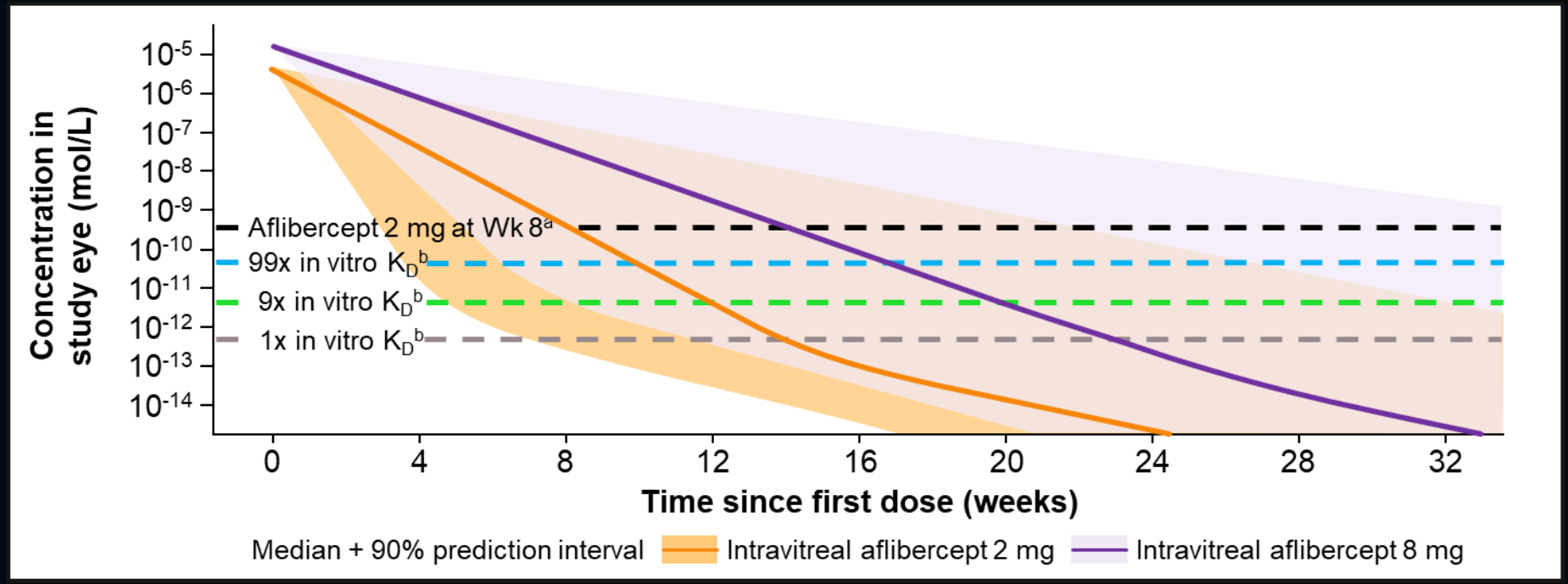
Model-estimated Ocular Clearance of Aflibercept 8-mg and 2-mg Drug Products

	Aflibercept 2 mg	Aflibercept 8 mg
Ocular clearance, mL/day	0.625	0.410

- The PopPK model-estimated ocular clearance was **34.4% slower for the aflibercept 8-mg vs 2-mg drug product** and was attributed to an aflibercept 8-mg drug product effect

PopPK-simulated Free Aflibercept Concentrations in the Ocular Compartment Relative to Reference Concentrations[a,b]

- Median free aflibercept ocular concentration is estimated to remain above reference concentrations **6 to 8.9 weeks longer** for the aflibercept 8-mg versus 2-mg drug product

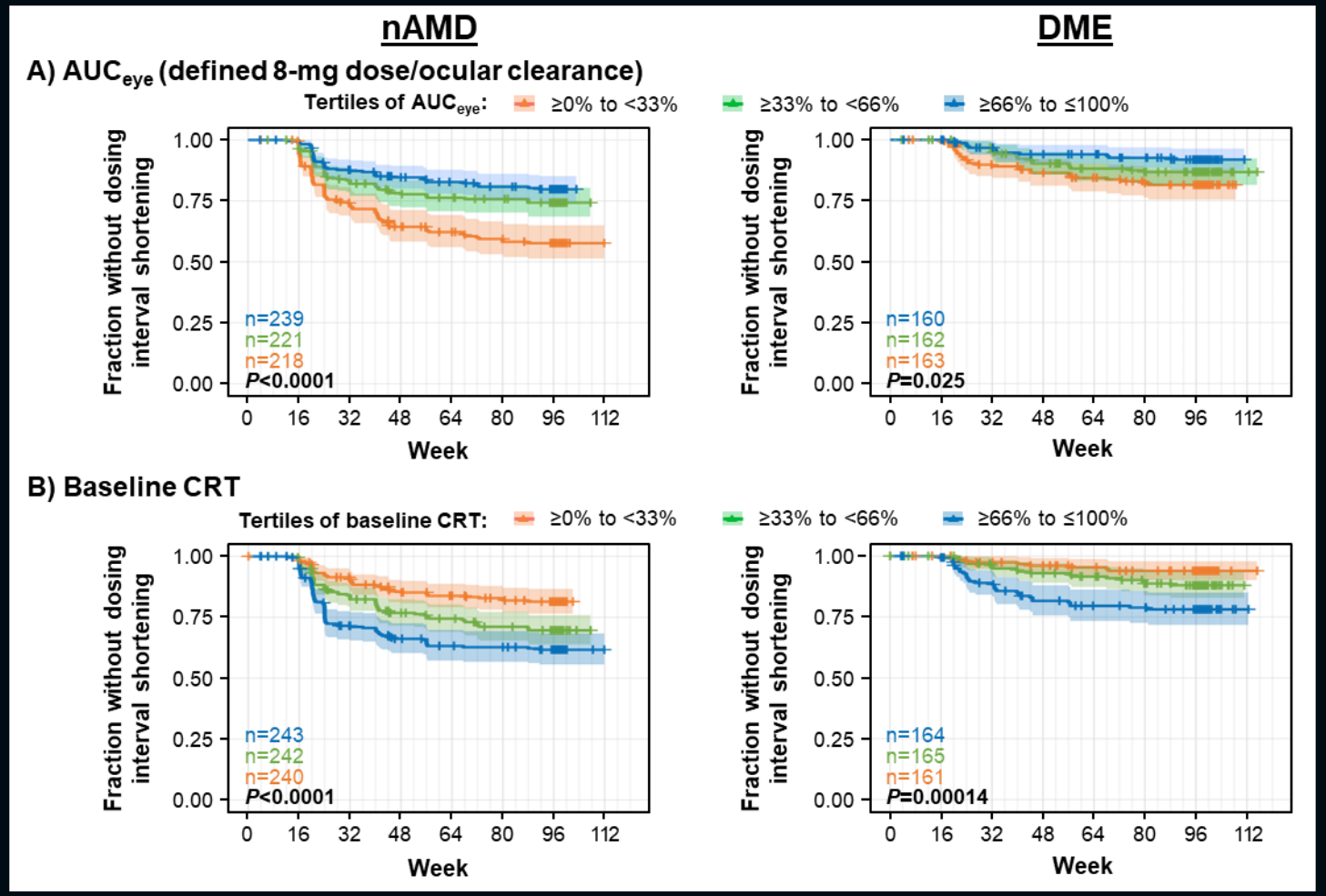


- **49.5% of virtual patients** are estimated to maintain free aflibercept ocular concentration above 9x the in vitro K_D for binding to VEGF-A for 20 weeks for aflibercept 8-mg

[a]Concentration of free aflibercept, following intravitreal injection, at the end of an 8-week dosing interval with aflibercept 2 mg estimated by the PopPK modeling.
[b]Concentrations were set as 1x, 9x, and 99x the K_D values representing the free aflibercept concentrations required to inhibit VEGF-A by 50%, 90%, or 99% in an in vitro setting.
K_D, dissociation constant of in vitro aflibercept binding to VEGF-A; VEGF-A, vascular endothelial growth factor-A (K_D=0.497 pM); Wk, week.

Time to First Dosing Interval Shortening With Aflibercept 8 mg in Patients With nAMD[a,b] or DME[c]

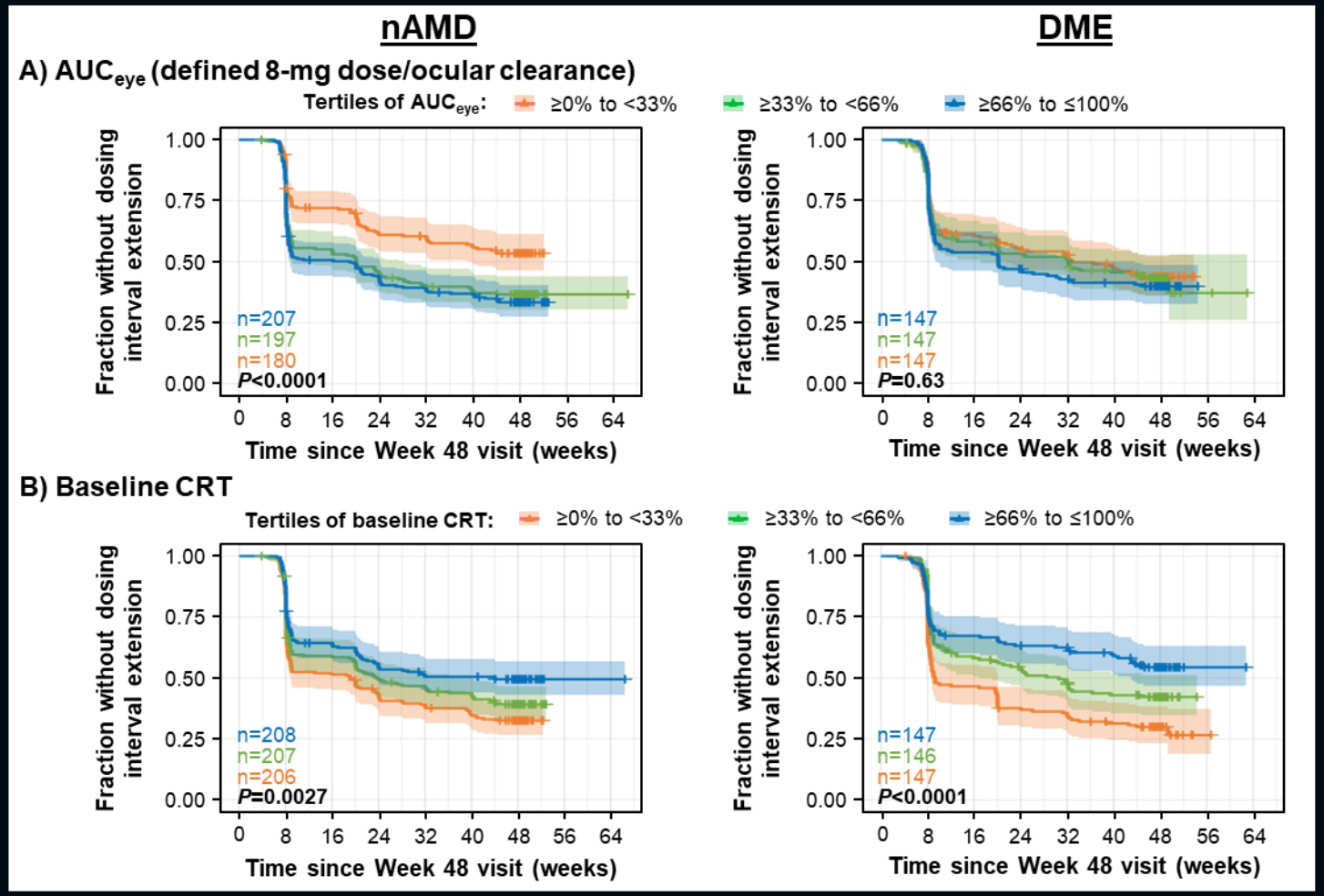
- In patients with nAMD or DME, the **rate of dosing interval shortening increased** as tertile of:
  - **AUC_{eye} decreased** (or as ocular clearance increased)
  - **Baseline CRT increased**



In panel A, data from 48 patients with nAMD and 6 patients with DME and imputed ocular distribution clearance are not shown. In panel B, data from 1 patient with nAMD and 1 patient with DME and imputed baseline CRT are not shown.
P-values were calculated using standard log-rank tests that evaluated differences across treatment groups.
[a]In CANDELA, aflibercept 8 mg–treated patients could have received additional treatment at Week 16 because of persistent or worsening nAMD and PRN treatment at Weeks 24, 28, 36, and 40 if they lost ≥5 letters in BCVA from Week 20 due to disease progression OR had vision-threatening anatomic findings, per investigator judgment, such as worsening or persistent retinal fluid, new or worsening retinal pigment epithelial detachment, or new or persistent hemorrhage.[1,5] [b]From Week 16 of PULSAR, dosing intervals of aflibercept 8 mg–treated patients were shortened if they had >5-letter loss in BCVA from Week 12 due to persistent or worsening nAMD AND >25-µm increase in CRT from Week 12 OR new-onset foveal neovascularization OR foveal hemorrhage.[2,3] [c]From Week 16 of PHOTON, dosing intervals of aflibercept 8 mg–treated patients were shortened if they had >10-letter loss in BCVA from Week 12 due to persistent or worsening DME AND >50-µm increase in CRT from Week 12.[4,5]
1. Wykoff CC et al. *JAMA Ophthalmol.* 2023;141:834–842. 2. Lanzetta P et al. *Lancet.* 2024;403:1141–1152. 3. Korobelnik JF. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA. 4. Brown DM et al. *Lancet.* 2024;403:1153–1163.
5. Do DV. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA.
AUC_{eye}, area under the curve in the eye between 2 injections; CRT, central retinal thickness; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration.

Time to First Dosing Interval Extension With Aflibercept 8 mg in Patients With nAMD[a] or DME[b]

- In patients with nAMD or DME, the **rate of dosing interval extension increased** as tertile of:
  - **AUC_{eye} increased** (or as ocular clearance decreased)
  - **Baseline CRT decreased**



In panel A, data from 37 patients with nAMD and imputed AUC_{eye} are not shown. In panel B, data from 1 patient with DME and imputed baseline CRT are not shown.
P-values were calculated using standard log-rank tests that evaluated differences across treatment groups.
[a]From Week 52 of PULSAR, dosing intervals of aflibercept 8 mg–treated patients were extended if they had <5-letter loss in BCVA from Week 12 AND no fluid at the central subfield on optical coherence tomography AND no new-onset foveal hemorrhage or foveal neovascularization.[1] [b]From Week 52 of PHOTON, dosing intervals of aflibercept 8 mg–treated patients were extended if they had <5-letter loss in BCVA from Week 12 AND CRT <300 µm (or <320 µm on Spectralis).[2]
1. Korobelnik JF. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA. 2. Do DV. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA.
AUC_{eye}, area under the curve in the eye between 2 injections; CRT, central retinal thickness; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration.

Conclusions

- PopPK modeling and simulation estimated a 34.4% slower ocular clearance and 6- to 8.9-week longer maintenance of free aflibercept concentrations above reference concentrations in the eye the aflibercept 8-mg versus 2-mg drug product, consistent with the longer durability of effect observed for aflibercept 8 mg in clinical trials
- Exposure-response modeling consistently showed that AUC_{eye} for free aflibercept (inversely correlated with ocular clearance) and baseline CRT contributed to both dosing interval shortening and extension in the aflibercept 8-mg trials
  - These data provide insight into why some patients require dosing as frequently as every 8 weeks whereas others can maintain visual and anatomic improvements with dosing intervals of 20 weeks or longer
  - Disease progression, comorbidities, and variability in treatment response also influence the need for dosing interval modification