Population Pharmacokinetic Modeling and Simulation of Ocular Clearance for Aflibercept 8 mg vs 2 mg and Associated Durability of Effect

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Presented at the American Academy of Ophthalmology Meeting, October 18–21, 2024

Disclosures

- Michael W. Stewart is a consultant for Bayer, Biogen, and Revana and has received research support from Alexion
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). This analysis was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY). The sponsors participated in the design and conduct of this analysis, data interpretation, and preparation of this presentation
- Trials include research conducted on human patients. Institutional Review Board approval was obtained prior to initiation of each trial
- Writing assistance was provided by Caryn Trbovic, PhD, of Regeneron Pharmaceuticals, Inc.

Background

- The aflibercept 8-mg drug product is a novel formulation that delivers a molar dose 4 times that of aflibercept 2 mg,[1] enabling sustained inhibition of VEGF signaling in the eye
- At Week 48 of the PULSAR and PHOTON trials in nAMD and DME, respectively, aflibercept 8q12 and 8q16 after 3 monthly doses demonstrated non-inferior BCVA gains to aflibercept 2q8 after 3 (PULSAR) or 5 (PHOTON) monthly doses[2,3]
  - Aflibercept 8q12 and 8q16 maintained similar BCVA gains to those of 2q8 through Week 96 in both trials[4,5]
- The aflibercept 2-mg (40 mg/mL) and 8-mg (114.3 mg/mL) drug products are distinct formulations with different excipients
- It is important to characterize the pharmacokinetic properties that support the extended duration of effect of aflibercept 8 mg versus 2 mg observed in clinical trials

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

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; VEGF, vascular endothelial growth factor.

1. Wykoff CC et al. *JAMA Ophthalmol*. 2023;141:834–842. 2. Lanzetta P et al. *Lancet*. 2024;403:1141–1152. 3. Brown DM et al. *Lancet*. 2024;403:1153–1163. 4. Korobelnik JF. Aflibercept 8 mg in patients with neovascular AMD: phase 3 PULSAR trial 96-week results. Presented at: American Academy of Ophthalmology; November 3-6, 2023; San Francisco, CA. 5. Do DV. Aflibercept 8 mg for diabetic macular edema: 96-week results from the phase 2/3 PHOTON trial. Presented at: American Academy of Ophthalmology; November 3-6, 2023; San Francisco, CA.

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:

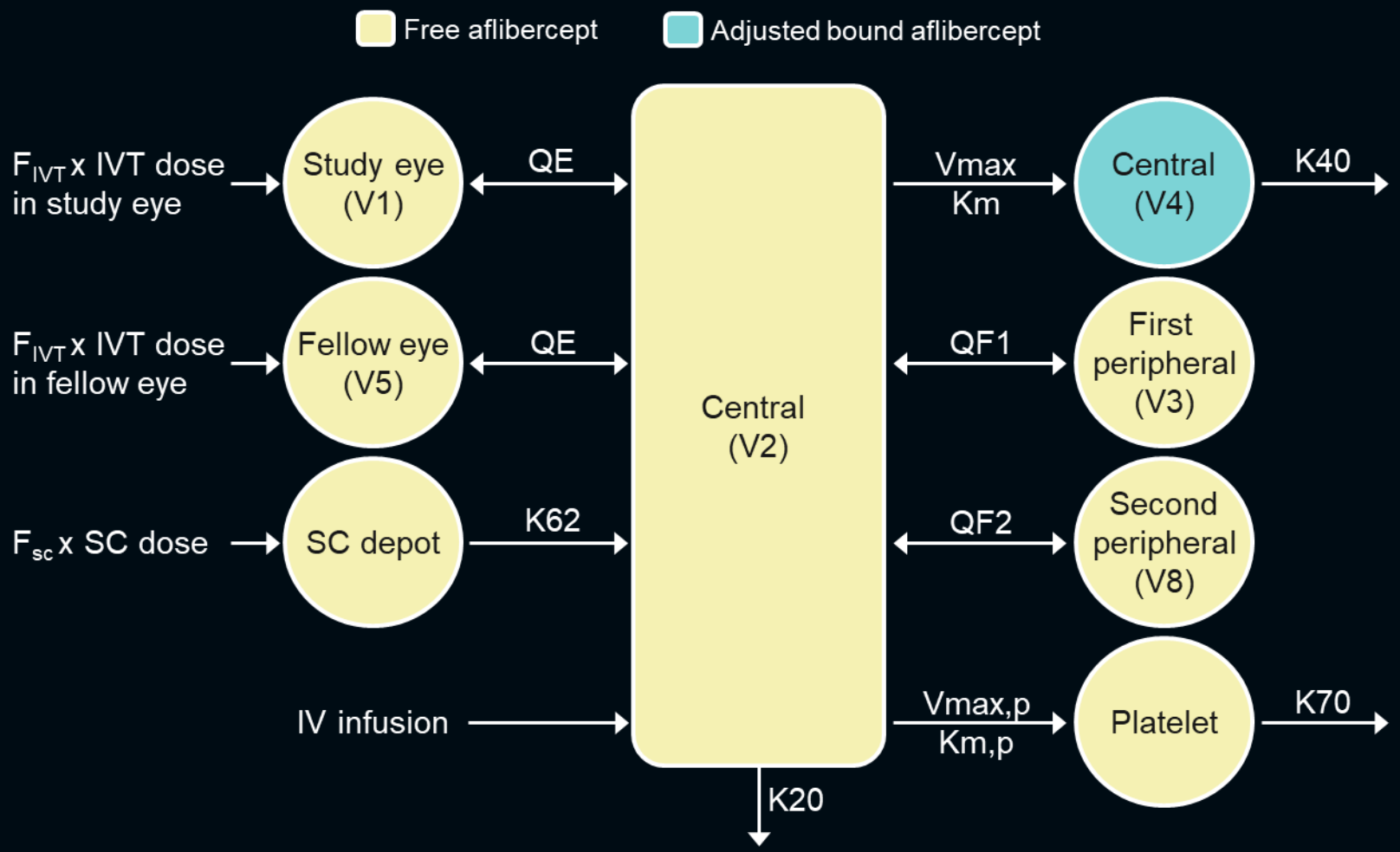
      726 patients with nAMD (CANDELA and PULSAR) and **491 patients with DME** (PHOTON)
    - Time to first dosing interval extension model:

      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.

Population Pharmacokinetic Modeling and Simulation

Final PopPK Model for IV, SC, and IVT Administration of Aflibercept



FIVT, bioavailability after intravitreal injection in the study eye; FSC, bioavailability after SC injection; IV, intravenous; IVT, intravitreal; K20, elimination rate constant for free aflibercept; K40, elimination rate constant for adjusted bound aflibercept; K62, absorption rate constant of free aflibercept from SC depot compartment; K70, elimination rate constant of free aflibercept from the platelet compartment; Km, concentration of free aflibercept at half of maximum binding capacity with VEGF; Km,p, concentration of free aflibercept at half of maximum binding capacity to platelets; QE, ocular distribution clearance; QF1, first distribution clearance for free aflibercept; QF2, second distribution clearance for free aflibercept; SC, subcutaneous; V1, volume of the study eye; V2, volume of the central compartment for free aflibercept; V3, volume of the first peripheral compartment for free aflibercept; V4, volume of the central compartment for adjusted bound aflibercept; V5, volume of the fellow eye; V8, volume of the second peripheral compartment for free aflibercept; VEGF, vascular endothelial growth factor; Vmax, maximum binding rate of free aflibercept to VEGF; Vmax,p, maximum binding rate of aflibercept to platelets.

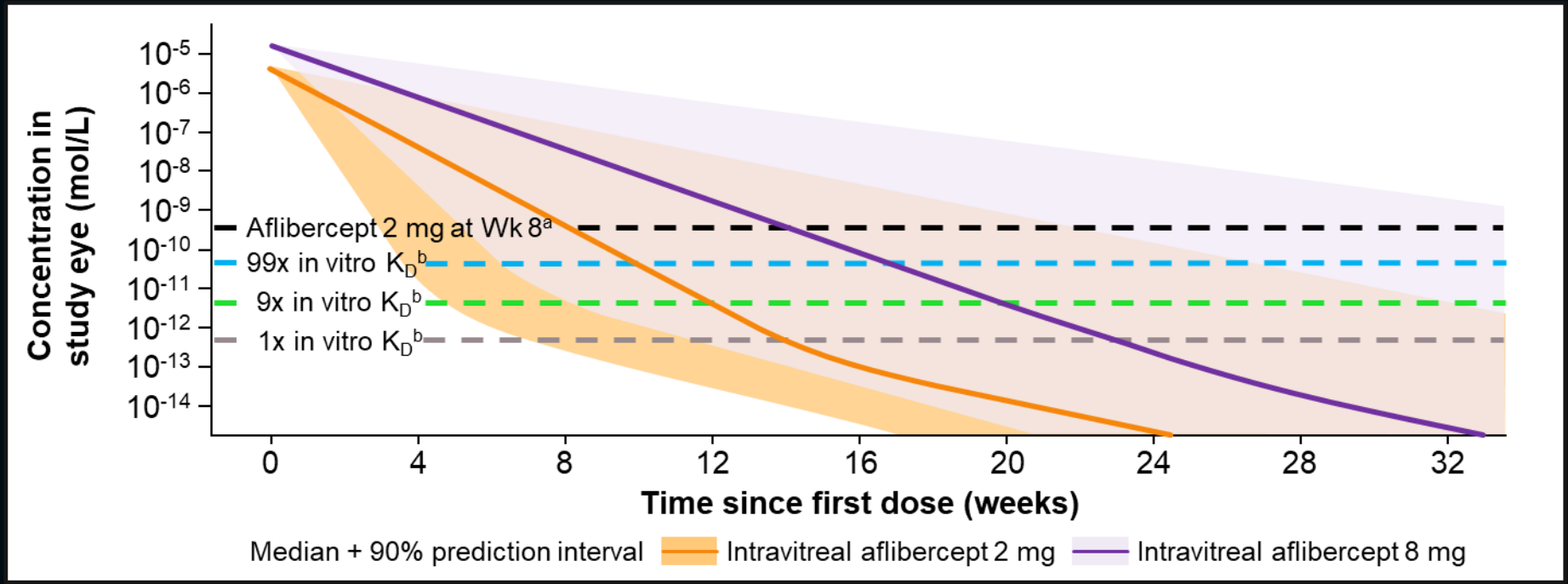
Model-estimated Ocular Clearance of Aflibercept 8-mg and 2-mg Drug Products

	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



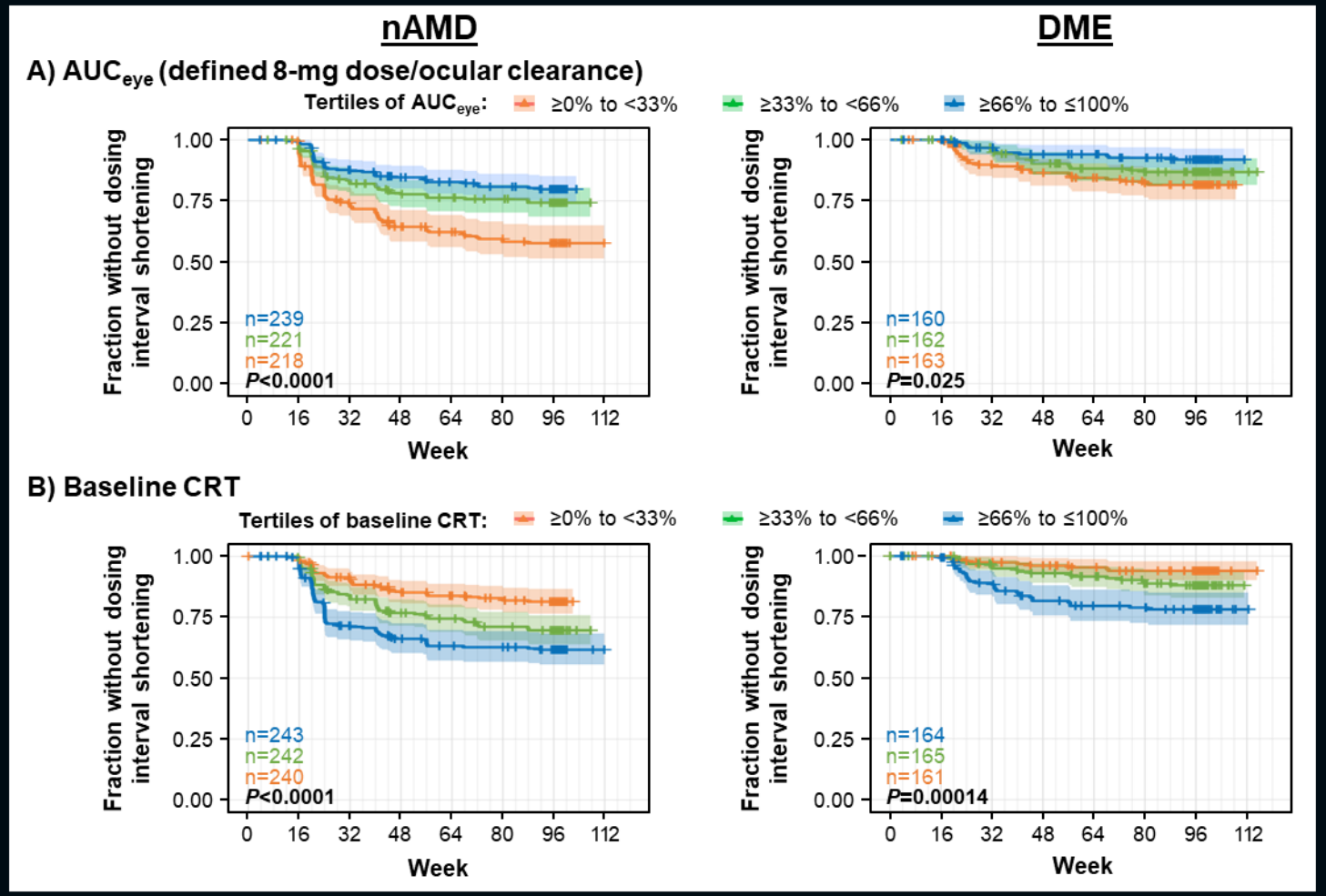
- For aflibercept 8-mg, **49.5% of virtual patients** are estimated to maintain free aflibercept ocular concentrations above 9x the in vitro K_D (binding constant of aflibercept to VEGF-A) for 20 weeks

[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.

Exposure-Response Modeling

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

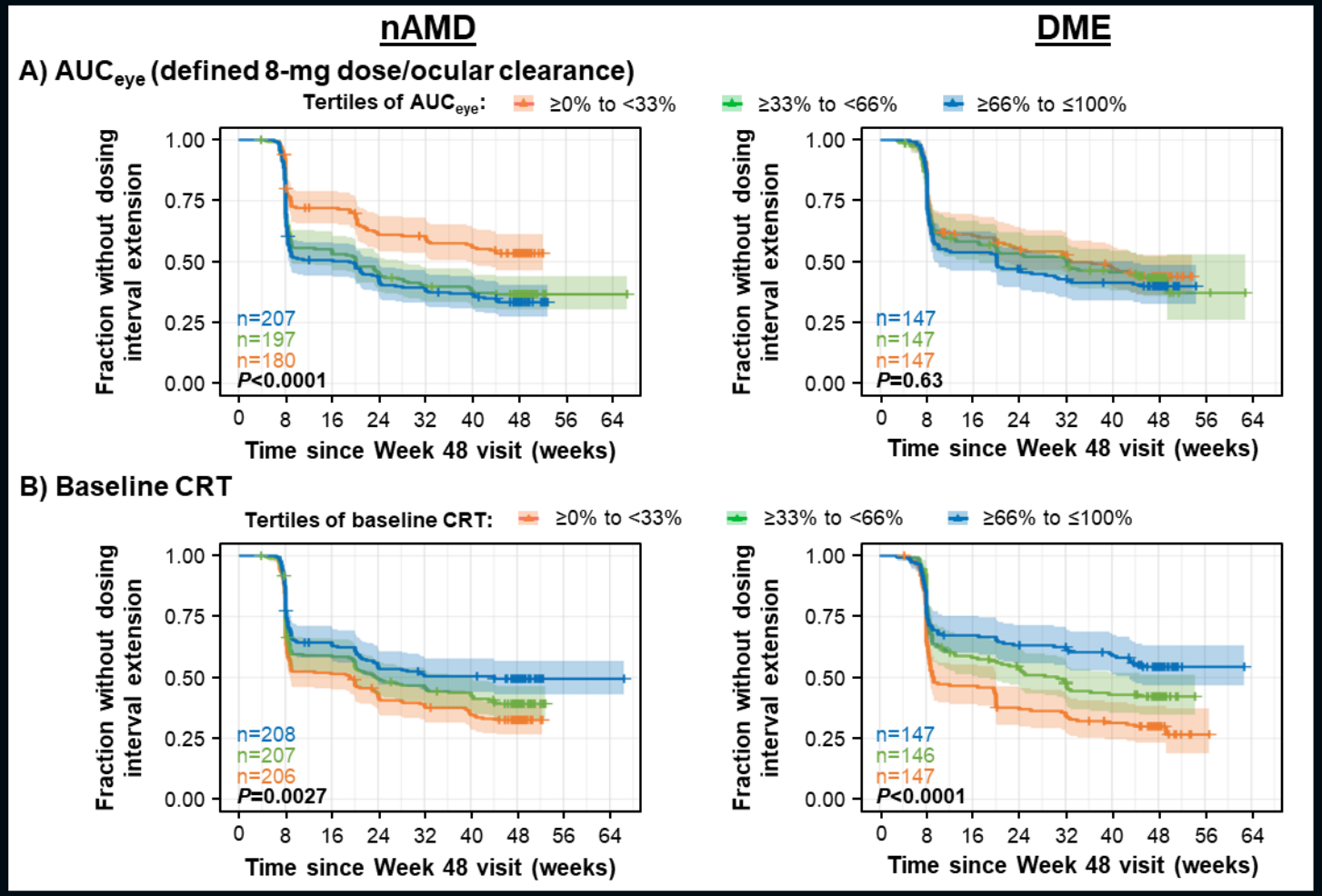
- In patients with nAMD or DME, the **rate of dosing interval shortening increased** as tertile of:
  - **AUC_{eye} decreased** (or as ocular clearance increased)
  - **Baseline CRT increased**



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]

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



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.

Limitations of the Research

- Population PK model-estimated ocular clearance of free aflibercept was derived using concentration data in plasma only; however:
  - Following intravitreal administration, the rate of free aflibercept elimination from the eye is much slower than its rate of elimination from plasma
  - As such, the rate of elimination of free aflibercept from plasma following intravitreal administration reflects its rate of elimination from the eye
  - This enables the elimination rate of free aflibercept from the eye to be modeled using concentration data in plasma only
- Simulated ocular concentrations are based on the eye being a single homogenous compartment and do not distinguish between concentrations in the aqueous or vitreous humor, or other compartments in the ocular space
- The PK and exposure response analyses assumed no change in ocular clearance
  - AUC_{eye} was derived from ocular clearance estimated from data collected during Year 1 but was assumed to be time-invariant over a 2-year span

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 for 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