Population Pharmacokinetic and Exposure-Response Analyses for Aflibercept

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BACKGROUND & PURPOSE

- Vascular endothelial growth factor (VEGF) is a key contributor to the pathophysiology of retinal vascular diseases such as neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME),[1] and intravitreal injections of anti-VEGF agents such as aflibercept are a standard treatment for patients with nAMD and DME[2,3]
- At Week 48 of the pivotal PULSAR and PHOTON trials in nAMD and DME, respectively, aflibercept 8 mg every 12 and 16 weeks (8q12 and 8q16) after 3 initial monthly doses demonstrated non-inferior best-corrected visual acuity (BCVA) gains to aflibercept 2 mg every 8 weeks (2q8) after 3 (PULSAR) or 5 (PHOTON) initial monthly doses[4,5]
  - Through Week 96 in both trials, the 8q12 and 8q16 groups maintained similar BCVA gains to those of the 2q8 group, and dosing intervals were maintained or extended in a large majority of patients in the 8q12 and 8q16 groups[6,7]
  - Dosing intervals were shortened in 29% (PULSAR) and 15% (PHOTON) of aflibercept 8 mg–treated patients through Week 96
- In this study, pharmacokinetic properties that support the extended duration of effect observed with aflibercept 8 mg versus 2 mg in clinical trials were characterized using population pharmacokinetic (PopPK) modeling and simulation
- Characteristics of aflibercept 8 mg–treated patients that may influence dosing interval shortening or extension were also evaluated using exposure-response modeling

METHODS

Aflibercept 8-mg Clinical Trial Overview

- In the Phase 2, 44-week CANDELA trial, aflibercept 8 mg–treated patients received treatment at Weeks 20 and 32 following 3 initial monthly doses, and an additional injection was administered per investigator discretion at Week 16 or PRN at Weeks 24, 28, 36, and 40 if patients met protocol-specified criteria[8]
- In the Phase 3 PULSAR and Phase 2/3 PHOTON trials, aflibercept 8-mg dosing intervals were shortened (beginning at Week 16) or extended (beginning at Week 52) by 4-week increments if patients met protocol-specified criteria[6,7]
  - The minimum dosing interval was every 8 weeks, and the maximum dosing interval was every 24 weeks[6,7]

PopPK Modeling and Simulation

- A previously described PopPK model[9] was extended to characterize the systemic and ocular disposition of aflibercept following intravenous, subcutaneous, or intravitreal administration
  - A semi-mechanistic PopPK model was developed based on free and adjusted bound aflibercept concentrations in plasma from 2744 individuals who received intravenous (0.3-4 mg/kg), subcutaneous (0.025-2 mg/kg), or intravitreal (0.05-8 mg) aflibercept treatment across 16 clinical trials, including intravitreal treatment in CANDELA, PULSAR, and PHOTON
- Free aflibercept concentrations were simulated over time in the ocular compartment for the intravitreal aflibercept 8-mg and 2-mg drug products for a combined population of 5000 virtual patients with nAMD and 5000 virtual patients with DME using patient characteristics randomly sampled from the analysis population and variability around the estimate of ocular clearance
  - Time above the model-estimated free aflibercept ocular concentration at the end of an 8-week dosing interval for aflibercept 2 mg, as well as free aflibercept ocular concentrations set at 1x, 9x, and 99x the dissociation constant of in vitro aflibercept binding to VEGF-A (K_D), was determined

Exposure-response Modeling

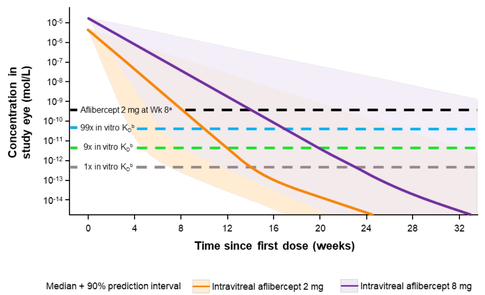
- Two distinct exposure-response models evaluating time to first dosing interval shortening and time to first dosing interval extension were developed to assess characteristics of aflibercept 8 mg–treated patients that may affect dosing interval shortening or extension
  - Time to first dosing interval shortening was based on data from 726 patients with nAMD (CANDELA and PULSAR) and 491 patients with DME (PHOTON)
  - Time to first dosing interval extension was based on data from 621 patients with nAMD (PULSAR) and 441 patients with DME (PHOTON)
- Both models were based on longitudinal dosing interval data, covariate information, and post hoc Bayesian PopPK estimates of ocular clearance from each patient
  - Longitudinal time to first dosing interval shortening or extension data were visualized with Kaplan-Meier plots
    - *P*-values were calculated using standard log-rank tests that evaluated differences across treatment groups
  - Cox proportional hazard models described time to first dosing interval shortening or extension events
- Age, sex, race, patient population, randomized dosing interval, baseline central retinal thickness (CRT), baseline BCVA, baseline hemoglobin A1c, duration of diabetes, cataract surgery, Japanese origin, study (for time to first dosing interval shortening only), and ocular clearance or area under the curve in the eye between 2 injections (AUC_{eye}, defined as 8-mg dose/ocular clearance) were evaluated as potential covariates in both models

RESULTS

PopPK Modeling and Simulation

- The PopPK model–estimated ocular clearance of free aflibercept was 34.4% lower than expected for the aflibercept 8-mg versus 2-mg drug product (0.410 vs 0.625 mL/day) and was attributed to an aflibercept 8-mg drug product effect
  - The composition of the aflibercept 8-mg formulation is unique, differing from that of aflibercept 2 mg with respect to pH, concentration, volume delivered, and excipients
- The time that median PopPK-simulated free aflibercept concentrations in the eye remained above reference concentrations (aflibercept 2 mg at Week 8 and multiples of in vitro K_D) was 6-8.9 weeks longer for the aflibercept 8-mg versus 2-mg drug product (**Figure 1**)
  - Simulations estimated that 49.5% of patients maintain free aflibercept ocular concentrations above 9x the in vitro K_D for 20 weeks after aflibercept 8-mg dosing
  - Findings are consistent with those of PULSAR and PHOTON in which 53% and 47% of patients in the 8q16 group, respectively, had their dosing intervals extended to ≥20 weeks through Week 96[6,7]

Figure 1. PopPK-simulated Concentrations of Free Aflibercept in the Ocular Compartment Relative to Reference Concentrations[a,b]



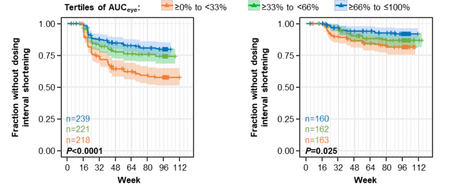
[a]Concentration of free aflibercept, following intravitreal injection, at the end of an 8-week dosing interval with aflibercept 2 mg estimated by PopPK modeling.
[b]Concentrations were set as 1x, 9x, and 99x the K_D values representing the free aflibercept concentrations required to inhibit VEGF-A by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

Exposure-response Modeling

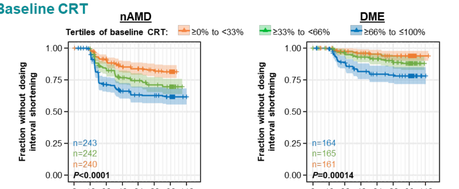
- Time to first dosing interval shortening increased as the AUC_{eye} (defined as 8-mg dose/ocular clearance) tertile decreased (or as ocular clearance increased) and as the baseline CRT tertile increased in patients with nAMD or DME (**Figure 2**)
  - Cox proportional hazard modeling estimated that the rate of dosing interval shortening was 38.7% lower for the 75th versus 25th percentile of AUC_{eye} for patients with identical baseline CRT (hazard ratio [HR] [95% CI]: 0.6130 [0.5137, 0.7314]; P=3.900e^{-16}) and 46.8% higher for the 75th versus 25th percentile of baseline CRT for patients with identical AUC_{eye} (HR [95% CI]: 1.468 [1.300, 1.658]; P=5.701e^{-10})
- Time to first dosing interval extension increased as AUC_{eye} tertile increased (or as ocular clearance decreased) in patients with nAMD and as baseline CRT decreased in patients with nAMD or DME (**Figure 3**)
  - Cox proportional hazard modeling estimated that the rate of dosing interval extension was 16.6% higher for the 75th versus 25th percentile of AUC_{eye} for patients with identical baseline CRT (HR [95% CI]: 1.166 [1.074, 1.266]; P =2.624e^{-4}) and 24.9% lower for the 75th versus 25th percentile of baseline CRT for patients with identical AUC_{eye} (HR [95% CI]: 0.7511 [0.6727, 0.8387]; P=3.536e^{-7})
- No trends were observed between other evaluated covariates and the rate of time to first dosing interval shortening or extension

Figure 2. Time to First Dosing Interval Shortening With Aflibercept 8 mg in Patients With nAMD[a,b] or DME[c] by Tertiles of (A) AUC_{eye} in the Study Eye and (B) Baseline CRT

A) AUC_{eye} (defined as 8-mg dose/ocular clearance)



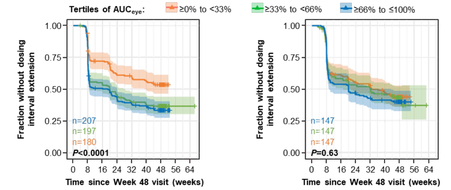
B) Baseline CRT



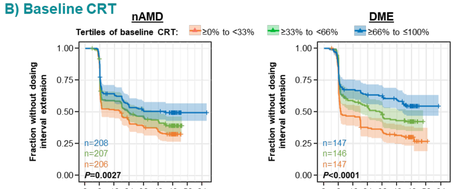
In panel A, data from 48 patients with nAMD and 6 patients with DME and imputed ocular distribution clearance are not shown. In panel B, data from 1 patient with nAMD and 1 patient with DME and imputed baseline CRT are not shown.
P-values were calculated using standard log-rank tests that evaluated differences 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.[8]
[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.[6,8]
[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.[6,7]

Figure 3. Time to First Dosing Interval Extension With Aflibercept 8 mg in Patients With nAMD[a] or DME[b] by Tertiles of (A) AUC_{eye} in the Study Eye and (B) Baseline CRT

A) AUC_{eye} (defined as 8-mg dose/ocular clearance)



B) Baseline CRT



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 patients 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.[6]
[b]From Week 52 of PHOTON, dosing intervals of aflibercept 8 mg–treated patients were extended if patients had <5-letter loss in BCVA from Week 12 AND CRT <300 µm (or <320 µm on Spectralis).[6]

CONCLUSIONS

- PopPK modeling estimated a 34.4% slower ocular clearance of free aflibercept for the aflibercept 8-mg versus 2-mg drug product, which was an unexpected finding and was attributed to an aflibercept 8-mg drug product effect
  - Model-based simulations estimated a longer median time above reference concentrations in the eye for the aflibercept 8-mg versus 2-mg drug product, which results from the higher dose and slower ocular clearance due to an aflibercept 8-mg drug product effect
  - Data from PopPK modeling and simulation provide additional support for the extension of aflibercept 8-mg dosing intervals up to every 20 weeks, or potentially longer, following 3 initial monthly doses in patients with nAMD or DME
- Results from 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 and 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
- Although findings from exposure-response analyses identified 2 patient characteristics that are associated with aflibercept 8-mg dosing interval shortening and extension, disease progression, comorbidities, and variability in treatment response can also influence the need for dosing interval modification

ACKNOWLEDGMENTS & DISCLOSURES

- David M. Brown serves as a scientific advisor for Regeneron/Bayer and Genentech/Roche and as a member of the Regeneron Combination Products Steering Committee
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of this poster
- Trials include research conducted on human patients. Institutional review board approval was obtained prior to initiation of each trial
- Medical writing support was provided by Stephanie Agbu, PhD, of Regeneron Pharmaceuticals, Inc.

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6. Korobelnik JF. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA.
7. Do DV. Presented at: American Academy of Ophthalmology; November 3, 2023; San Francisco, CA.
8. Wykoff CC et al. *JAMA Ophthalmol.* 2023;141:834–842.
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Poster presented by David M. Brown, MD, email: dmbmd@retinaconsultantstexas.com, at the ASRS 2024 Meeting, July 17–20, 2024

Methods

PopPK Modeling and Simulation

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  - A semi-mechanistic PopPK model was developed based on free and adjusted bound aflibercept concentrations in plasma from 2744 individuals who received intravenous (0.3-4 mg/kg), subcutaneous (0.025-2 mg/kg), or intravitreal (0.05-8 mg) aflibercept treatment across 16 clinical trials, including intravitreal treatment in CANDELA, PULSAR, and PHOTON
- Free aflibercept concentrations were simulated over time in the ocular compartment for the intravitreal aflibercept 8-mg and 2-mg drug products for a combined population of 5000 virtual patients with nAMD and 5000 virtual patients with DME using patient characteristics randomly sampled from the analysis population and variability around the estimate of ocular clearance

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- Two distinct exposure-response models evaluating time to first dosing interval shortening and time to first dosing interval extension were developed to assess characteristics of aflibercept 8 mg–treated patients that may affect dosing interval shortening or extension
- Both models were based on longitudinal dosing interval data, covariate information, and post hoc Bayesian PopPK estimates of ocular clearance from each patient
  - Longitudinal time to first dosing interval shortening or extension data were visualized with Kaplan-Meier plots
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- Age, sex, race, patient population, randomized dosing interval, baseline CRT, baseline BCVA, baseline hemoglobin A1c, duration of diabetes, cataract surgery, Japanese origin, study (for time to first dosing interval shortening only), and ocular clearance or area under the curve in the eye between 2 injections (AUC_{eye}, defined as 8-mg dose/ocular clearance) were evaluated as potential covariates in both models

AUC_{eye}, area under the curve in the eye between 2 injections; BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; PopPK, population pharmacokinetic.

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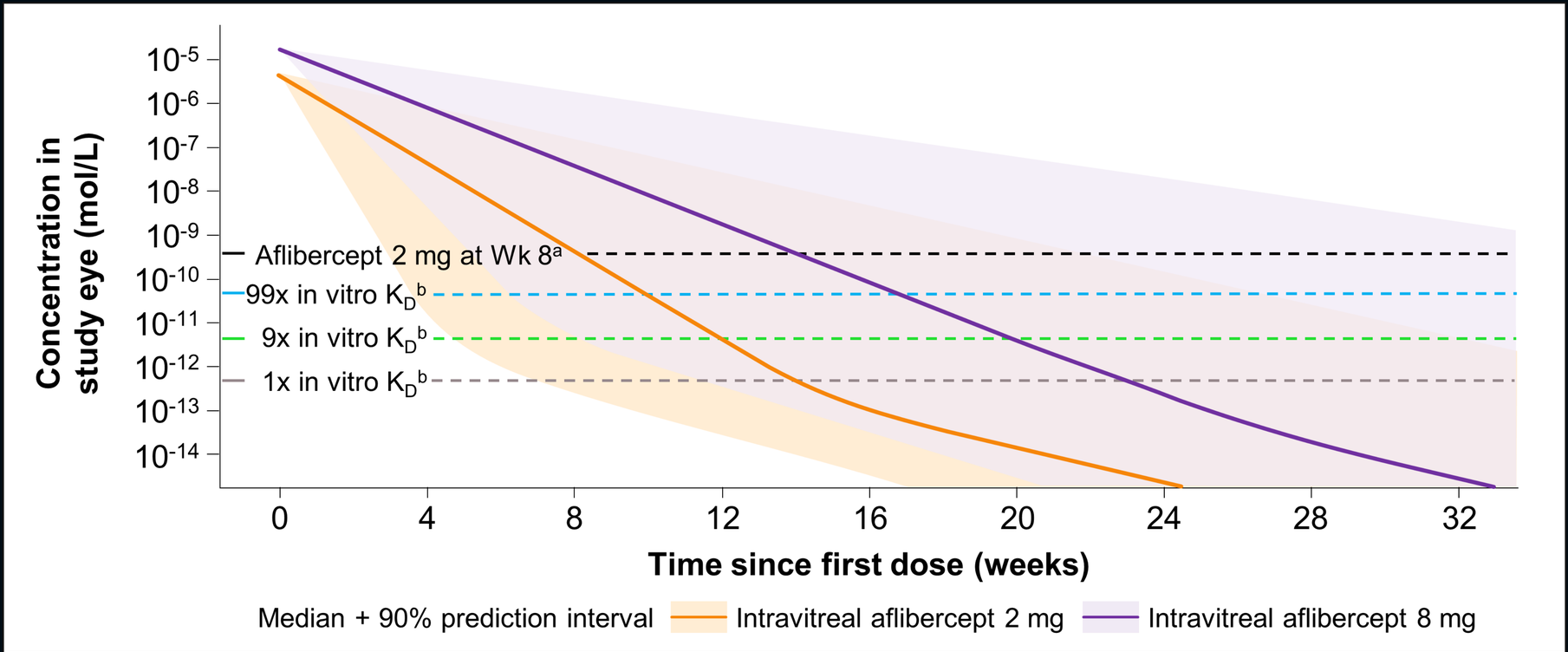
PopPK-simulated Free Aflibercept Concentrations in the Ocular Compartment Relative to Reference Concentrations[a,b]



- The time that median PopPK-simulated free aflibercept concentrations in the eye remained above reference concentrations (aflibercept 2 mg at Week 8 and multiples of in vitro K_D) was 6-8.9 weeks longer for the aflibercept 8-mg versus 2-mg drug product
- Simulations estimated that 49.5% of patients maintain free aflibercept ocular concentrations above 9x the in vitro K_D for 20 weeks after aflibercept 8-mg dosing

[a]Concentration of free aflibercept, following intravitreal injection, at the end of an 8-week dosing interval with aflibercept 2 mg estimated by PopPK modeling.
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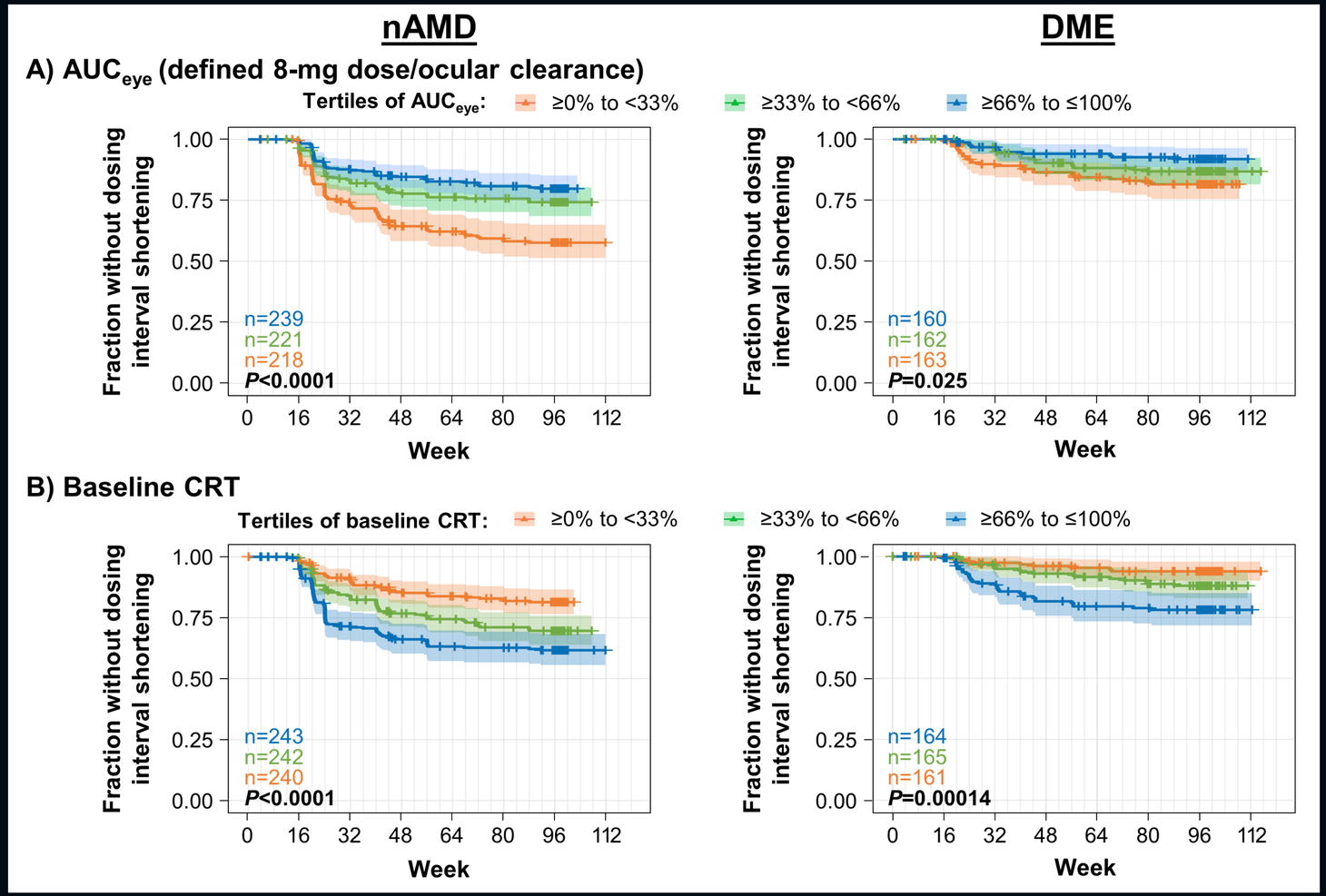
K_D, dissociation constant for free aflibercept binding to VEGF-A (K_D=0.497 pM); VEGF, vascular endothelial growth factor; Wk, week.

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

- Time to first dosing interval shortening increased as the AUC_{eye} (defined as 8-mg dose/ocular clearance) tertile decreased (or as ocular clearance increased) and as the baseline CRT tertile increased in patients with nAMD or DME
  - Cox proportional hazard modeling estimated that the rate of dosing interval shortening was 38.7% lower for the 75th versus 25th percentile of AUC_{eye} for patients with identical baseline CRT (P=3.900e^{-16}) and 46.8% higher for the 75th versus 25th percentile of baseline CRT for patients with identical AUC_{eye} (P=5.701e^{-10})



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- Time to first dosing interval extension increased as AUC_{eye} tertile increased (or as ocular clearance decreased) in patients with nAMD and as baseline CRT decreased in patients with nAMD or DME
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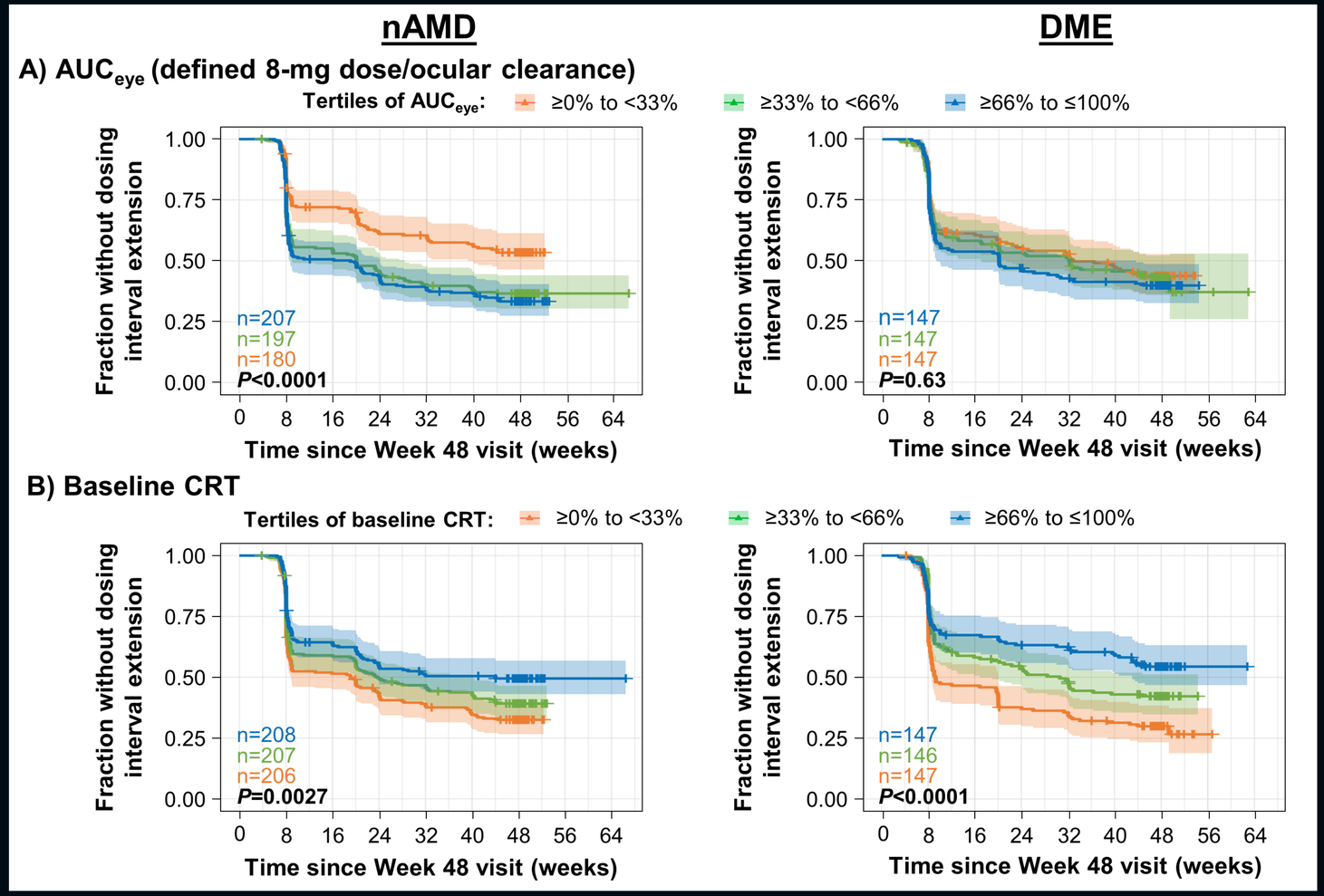

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