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

3154-A0441

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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]
  - Aflibercept was designed to bind with high affinity to VEGF and potently inhibit VEGF signaling[4,5]
- The aflibercept 8-mg drug product is a novel formulation that delivers a molar dose 4 times that of aflibercept 2 mg,[6] enabling sustained inhibition of VEGF signaling in the eye
- 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 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) monthly doses[7,8]
  - The aflibercept 8q12 and 8q16 groups maintained similar BCVA gains to those of the aflibercept 2q8 group through Week 96 in both trials[9,10]
- Findings at Week 48 of both trials supported regulatory approval of aflibercept 8 mg for the treatment of nAMD and DME in several countries, including the United States, those of the European Union, and Japan[11-13]
- To characterize pharmacokinetic properties that support the extended duration of effect observed with aflibercept 8 mg versus 2 mg in clinical trials, ocular clearance (QE) and time above reference concentrations in the eye (aflibercept 2 mg at Week 8 and multiples of in vitro K_D) were evaluated using population pharmacokinetic (PopPK) modeling and simulation

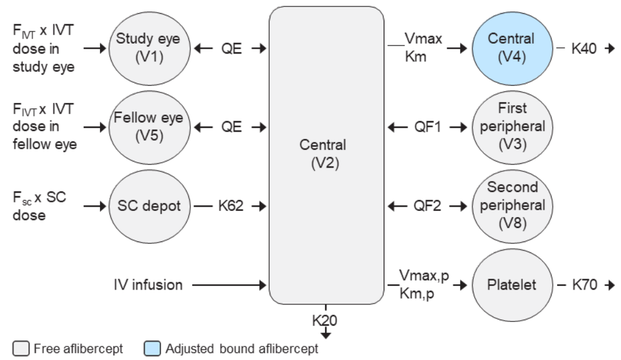
METHODS

- A previously described 2-compartment PopPK model for free and adjusted bound aflibercept concentrations in plasma[14] was extended to characterize the systemic and ocular disposition of aflibercept following intravenous, subcutaneous, or intravitreal administration
  - The new 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 the Phase 2 CANDELA trial, Phase 3 PULSAR trial, and Phase 2/3 PHOTON trial
  - Aflibercept 2-mg (40 mg/mL) and 8-mg (114.3 mg/mL) drug products are distinct formulations with different excipients
- The concentration of free aflibercept in the ocular compartment was simulated over time 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

RESULTS

- The final semi-mechanistic PopPK model describing the disposition of free and adjusted bound aflibercept comprised processes including nonlinear binding to VEGF, a first-order elimination rate from the central compartment (K20), and an additional nonlinear elimination pathway hypothesized to represent the saturable uptake of anti-VEGF proteins, such as aflibercept, by circulating platelets as reported in the literature[15] (**Figure 1**)

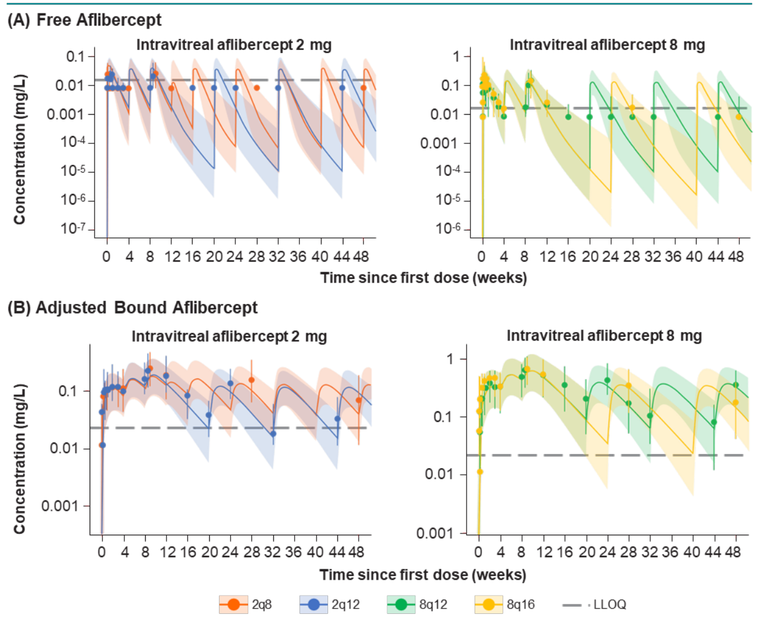
Figure 1. Structural Representation of PopPK Model for Intravenous, Subcutaneous, and Intravitreal Administration of Aflibercept



F_{IVT}, bioavailability after intravitreal injection in the study eye; F_{sc} 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; Vmax, maximum binding rate of free aflibercept to VEGF; Vmax,p, maximum binding rate of aflibercept to platelets.

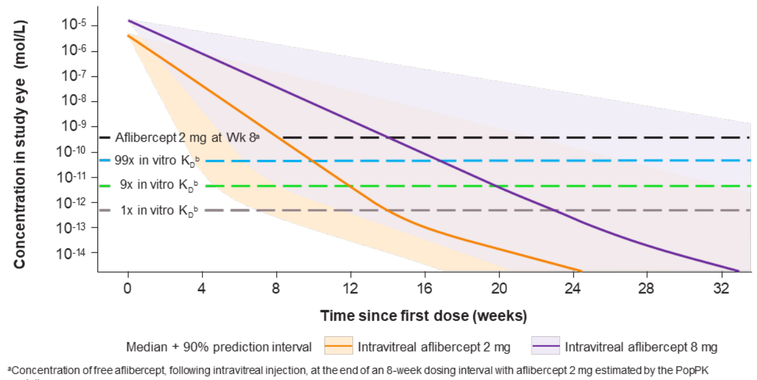
- The PopPK model adequately described data from the CANDELA, PULSAR, and PHOTON trials and was deemed appropriate for the characterization of PK and the derivation of PK parameter estimates (**Figure 2**)
- The PopPK model-estimated QE of free aflibercept was 34.4% lower than expected for the aflibercept 8-mg versus 2-mg drug product (0.410 versus 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 3**)
  - 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
    - These findings are consistent with those of the PULSAR and PHOTON trials in which 53% and 47% of patients in the 8q16 group, respectively, were able to extend their treatment interval to ≥20 weeks through Week 96[9,10]

Figure 2. Overlay of Observed and Model-based Stochastic Predictions of Plasma Concentrations of Free and Adjusted Bound Aflibercept for Patients With DME or nAMD



Points and error bars are medians and 90% confidence intervals of observed data. Lines and shaded areas are medians and 90% prediction intervals of simulated data.
2q12, aflibercept 2 mg every 12 weeks; LLOQ, lower limit of quantitation.

Figure 3. 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 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 for free aflibercept binding to VEGF-A (K_D=0.497 pM); Wk, week.

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 6- to 8.9-week 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 the aflibercept 8-mg drug product effect
- Consistent with the extended durability of effect observed for aflibercept 8 mg versus 2 mg in clinical trials, the PopPK model estimated that 49.5% of patients maintained free aflibercept ocular concentrations above 9x the in vitro K_D for 20 weeks following aflibercept 8-mg dosing
- Collectively, these data 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 and DME

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ACKNOWLEDGMENTS & DISCLOSURES

- Peter K. Kaiser is an employee of Ocular Therapeutix and a consultant for 4D Molecular Therapeutics, Alcon, Allergan, Bausch and Lomb, Bayer, Biogen Idec, Boehringer Ingelheim, Carl Zeiss Meditec, Coherus, Genentech/Roche, Kanghong, Kodiak, Novartis, Regeneron Pharmaceuticals, Inc., REGENXBIO, and Samsung Bioepis. Kenneth C. Turner, Sébastien Bihorel, Joannellyn Chiu, Lutz Harnisch, Jason Chittenden, and A. Thomas DiCioccio are employees and shareholders of Regeneron Pharmaceuticals, Inc. Thomas Eissing, Joachim Höchel, and Torsten Zimmermann are employees and shareholders of Bayer AG
- 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, Regeneron Pharmaceuticals, Inc.