

Pharmacokinetic/Pharmacodynamic Modeling and Simulation to Characterize Patients Who May Benefit from Monthly Dosing with Aflibercept 8 mg

Authors: Alejandro Perez-Pitarch (1), Sébastien Bihorel (1), Kenneth Turner (1), Joachim Hoechel (2), Thomas Eissing (3), John Davis (1), Lutz Harnisch (1)

Affiliations: (1) Regeneron Pharmaceuticals, Inc. Tarrytown, New York, USA, (2) Bayer AG, Berlin, Germany, (3) Bayer AG, Leverkusen, Germany.



INTRODUCTION

Aflibercept is a fully human recombinant fusion protein that acts as a soluble trap for vascular endothelial growth factor and inhibits its binding to and activation of endogenous receptors. Findings from the pivotal PULSAR [1] and PHOTON [2] trials supported the regulatory approval of aflibercept 8 mg for neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME) in several countries, including those of the European Union, Japan, and the United States, where it is also approved for diabetic retinopathy.

In the pivotal PULSAR and PHOTON studies for nAMD and DME, respectively, patients were randomized to aflibercept 8 mg every 12 or 16 weeks following 3 initial monthly doses. Per protocol, the minimum dosing interval permitted was 8 weeks (Q8). An exploratory post hoc analysis found that 6.2% of patients in the PULSAR study and 1.5% of patients in the PHOTON study continued to meet the criteria for dosing interval shortening after receiving the protocol minimum dosing interval of Q8.

OBJECTIVE

The primary objective of this analysis was to reveal the characteristics of patients with DME or nAMD who could have benefited from aflibercept 8 mg Q4 in the PULSAR and PHOTON studies, and to infer the benefit they would have experienced.

CONCLUSIONS

This analysis found high baseline CRT and fast Q_E to be associated with the need for more frequent dosing (i.e. Q4 dosing). Model-based simulations inferred that patients in PULSAR and PHOTON who had their dosing interval shortened to the protocol-specified minimum of Q8 and continued to meet interval shortening criteria may have benefited from Q4 dosing.

REFERENCES

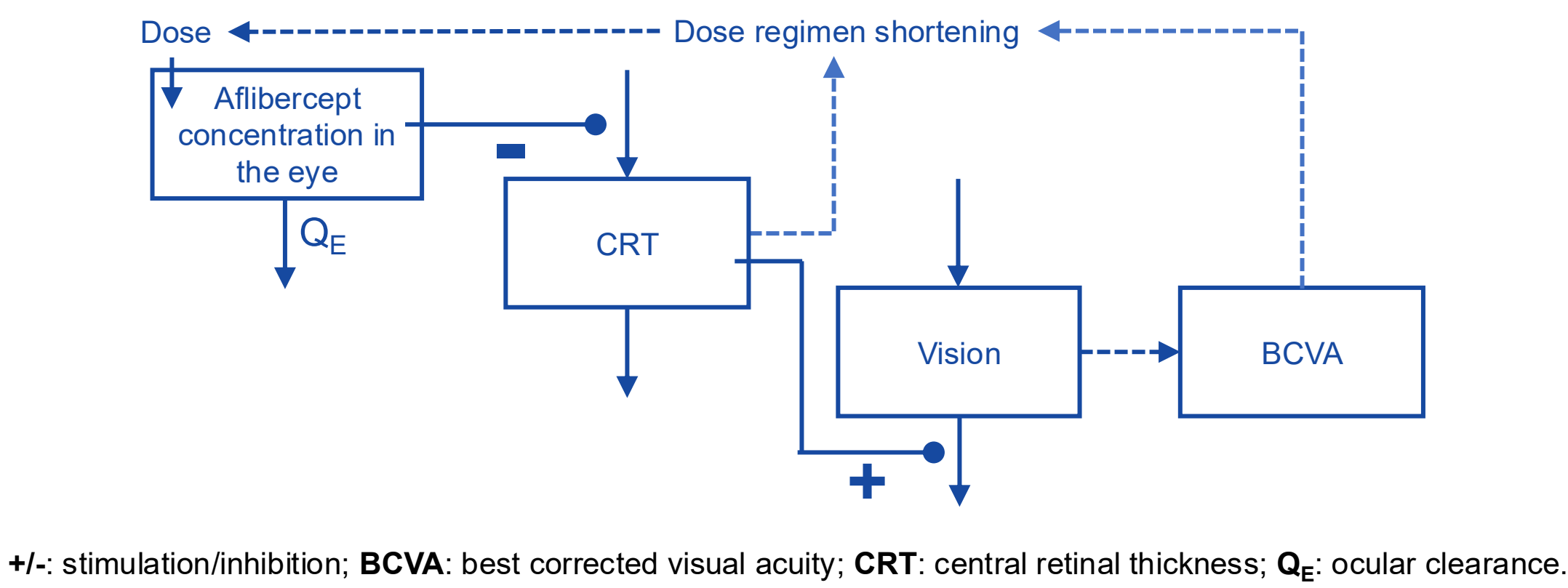
[1] Lanzetta P et al. *Lancet*. 2024;403:1141-1152.
[2] Brown DM et al. *Lancet*. 2024;403:1153-1163.
[3] NONMEM Users Guides. Ellicott City, MD: Icon Development Solutions; 1989-2009

METHODS

The analysis was limited to patients treated with aflibercept 8 mg in the PULSAR and PHOTON studies. Pharmacokinetic (PK)/pharmacodynamic (PD) models were developed in NONMEM [3] to characterize the relationship between aflibercept concentration in the eye, central retinal thickness (CRT) and best corrected visual acuity (BCVA) longitudinally (Figure 1 and Model Equations). Aflibercept concentrations in the eye (governed by ocular clearance [Q_E]) were utilized in this analysis to integrate the previously developed population PK model with the response of CRT and BCVA over time.

Simulations were performed to predict the impact of dosing interval adaptations (in response to changes in CRT and BCVA based on protocol-specified criteria from PULSAR and PHOTON) on treatment effect and clinical outcomes. In particular, the clinical benefit of shortening the dosing interval to Q4 in patients in PULSAR and PHOTON who had their dosing interval shortened to the protocol-specified minimum of Q8, but still continued to meet interval shortening criteria, was investigated. In addition, the clinical benefit of interval shortening to Q4 in virtual cohorts resembling theoretical future treated populations with nAMD or DME was investigated.

Figure 1. Schematic Representation of Structural PK/PD Model



+/-: stimulation/inhibition; BCVA: best corrected visual acuity; CRT: central retinal thickness; Q_E : ocular clearance.

RESULTS

Figure 2. Visual Predictive Check of CRT and BCVA Change from Baseline for the PHOTON Study, Stratified by Quartiles of Ocular Clearance Estimates and Considering the Full Joint Model and Dose Regimen Modifications

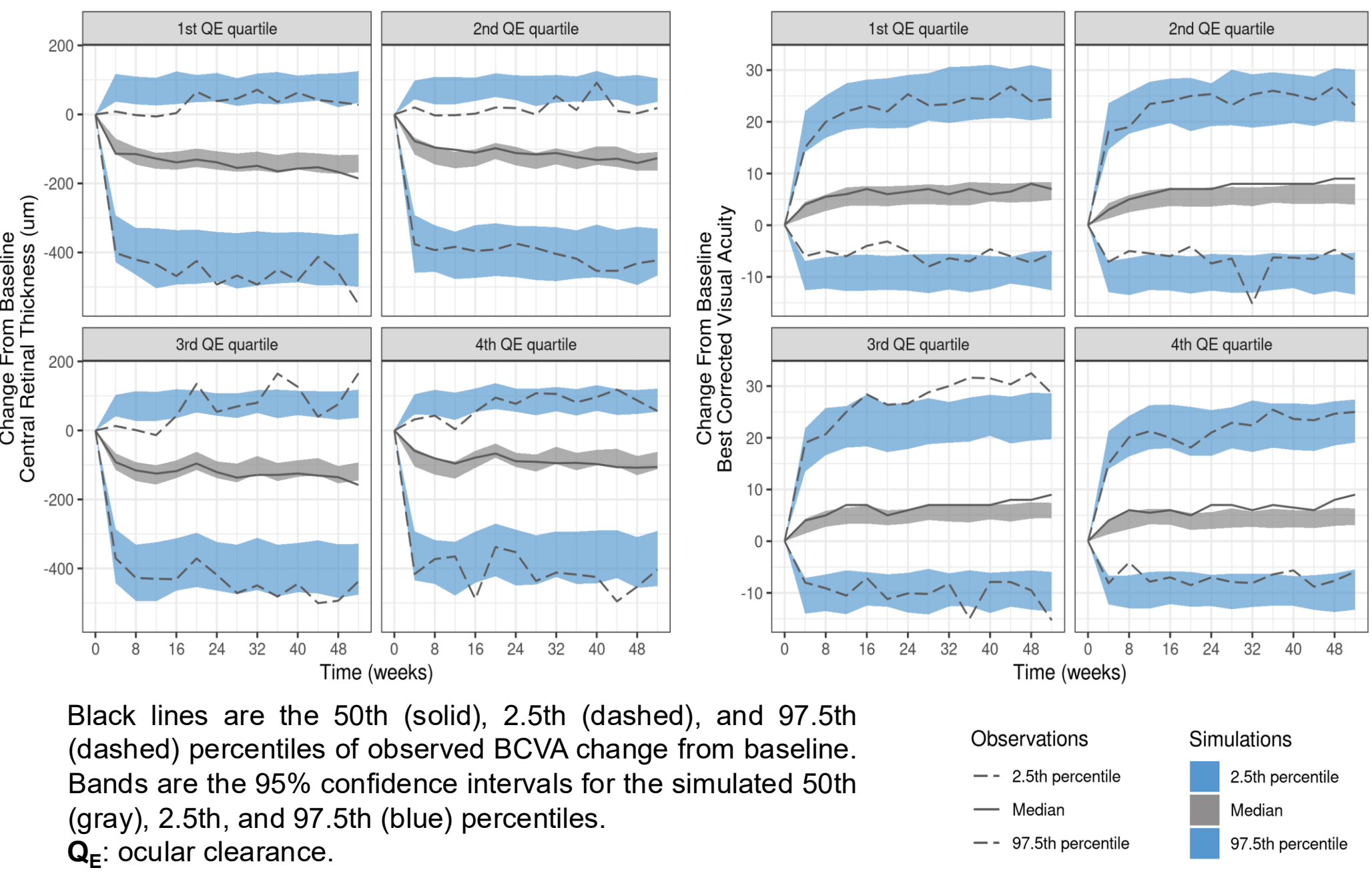
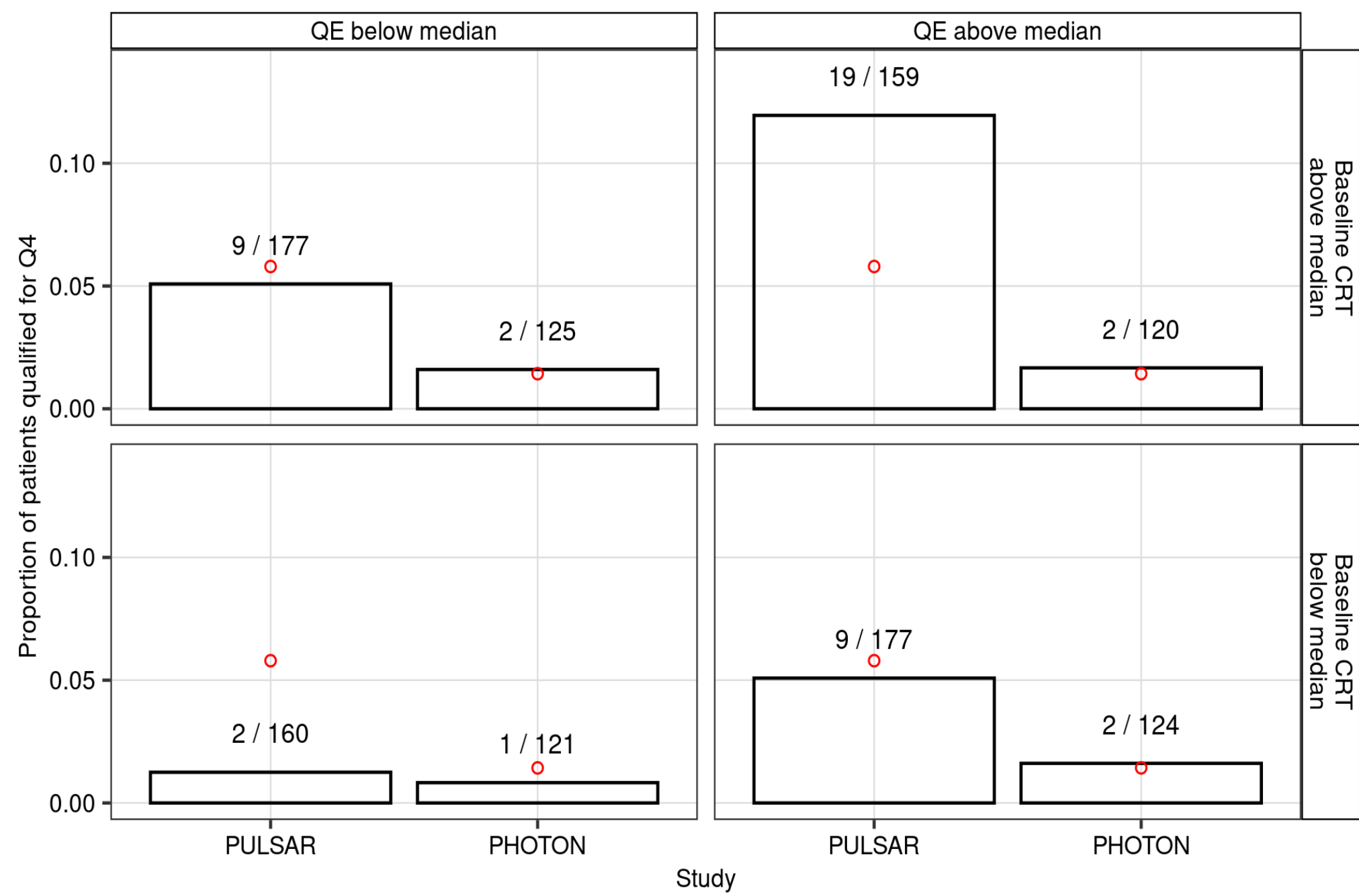


Figure 3. Incidence of Dosing Interval Shortening to Every 4 Weeks for Patients with Ocular Clearance Estimates and Baseline CRT Values Above and Below the Respective Medians



Red dots represent the proportion of patients that qualified for dosing every 4 weeks in each of the trials irrespective of the baseline central retinal thickness and the ocular clearance estimate. CRT: central retinal thickness; Q4: dosing every 4 weeks; Q_E : ocular clearance.

Model Equations

CRT

$$\frac{dCRT}{dt} = Kin_{CRT} - Kout_{CRT} \times CRT(t)$$
$$Kin_{CRT} = Kin_{CRT,0} \left(1 + \left(\frac{Kin_{CRT,MAX}}{Kin_{CRT,0}} - 1 \right) \times (1 - e^{-K_{CRT} \times C_{eye}(t)}) \right)$$
$$CRT_0 = \frac{Kin_{CRT}}{Kout_{CRT}}$$

Vision

$$\frac{dVision}{dt} = Kin_{Vision} - Kout_{Vision} \times Vision(t)$$
$$Kout_{Vision} = Kout_{Vision,0} \times e^{\left(\frac{CRT-140}{CRT_0-140} - 1 \right) \times K_{Vision}}$$
$$Vision_0 = e^{(CRT_0-450) \times K_{CRT,Vision}}$$

BCVA

$$BCVA = 100 \times \frac{Vision}{Vision_{50} + Vision}$$

C_{eye} : aflibercept concentration in the eye; CRT: central retinal thickness; CRT₀: baseline CRT; K_{CRT} : drug effect coefficient; $K_{CRT,Vision}$: coefficient governing the effect of CRT at baseline on the $Vision_{50}$; K_{Vision} : coefficient governing the effect of CRT and CRT at baseline on $Kout_{Vision}$; Kin_{CRT} : zero order rate constant governing the input to CRT; $Kin_{CRT,0}$: zero order rate constant governing the input to CRT in the absence of aflibercept; $Kin_{CRT,MAX}$: zero order rate constant governing the input to CRT when maximum effect is achieved; Kin_{Vision} : zero-order rate constant governing the input to Vision; $Kout_{CRT}$: first order output constant governing the turnover rate of CRT; Vision: latent variable representing the underlying vision of the patient; $Kout_{Vision}$: first order output constant governing the turnover rate of vision; $Kout_{Vision,0}$: first order output constant governing turnover rate of vision at baseline; Vision₀: baseline vision; Vision₅₀: vision latent variable value that yields a BCVA score of 50.

Acknowledgements

The authors thank the patients, their families, all other investigators, and all investigational site members involved in this study. This analysis was funded by Regeneron Pharmaceuticals, Inc (Tarrytown, New York) according to Good Publication Practice (GPP) guidance (*Ann Intern Med*. 2022;175:1298–1304).

Responsibility for all opinions, conclusions, and data interpretation lies with the authors.