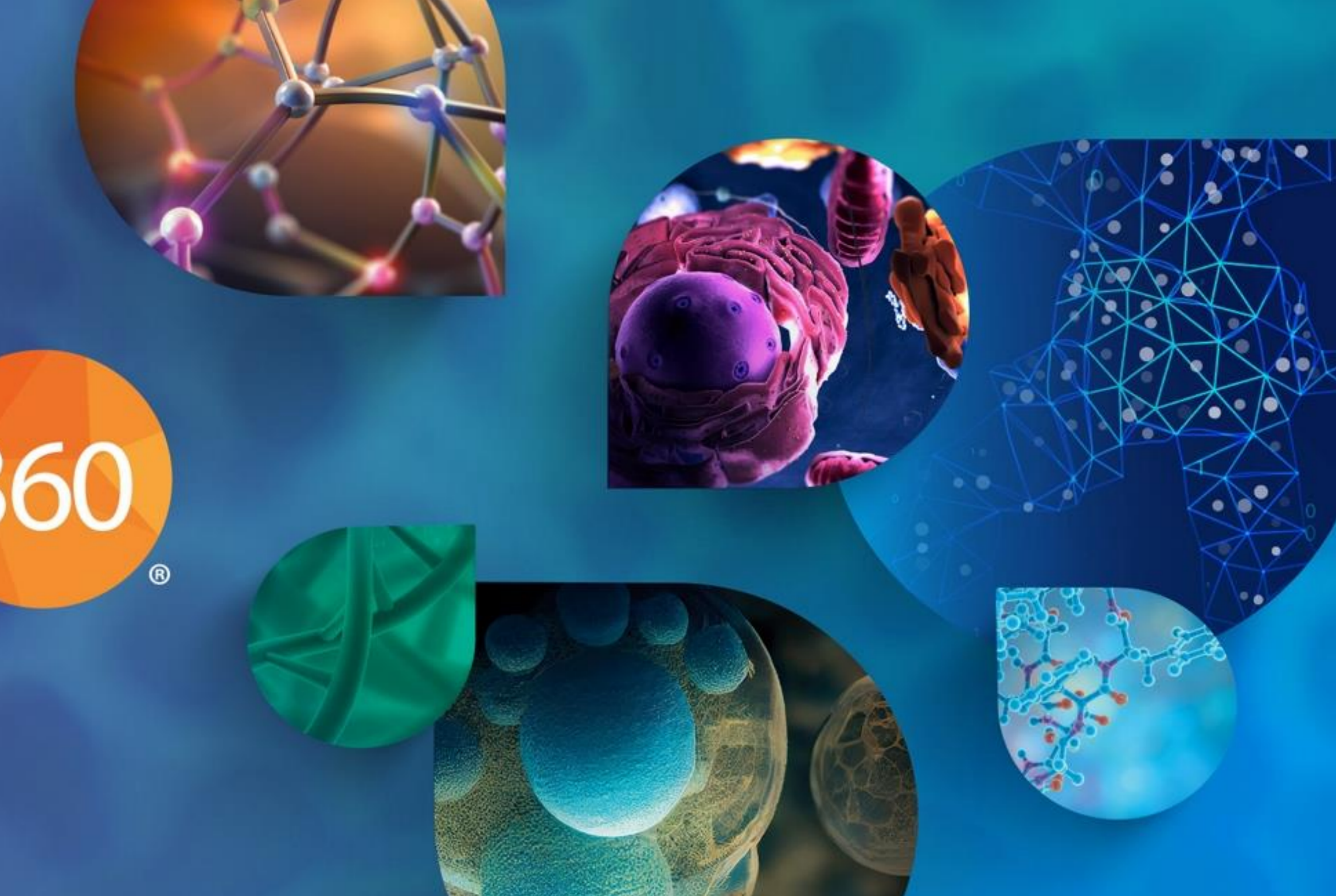


Predicting Aflibercept Local Exposure in Humans Using an Ocular PBPK Model

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PURPOSE

- Developing both innovative and generic ophthalmic drug products remains a significant hurdle for the pharmaceutical industry.
- Ocular physiologically based pharmacokinetic (O-PBPK) offer valuable insights into how drugs distribute across different eye tissues.
- O-PBPK models is an alternative approach for studying the ocular pharmacokinetics and pharmacodynamics.
- The utility of O-PBPK models has already been shown in predicting first-in-human doses for small molecule drugs.
- This study aims to demonstrate how an O-PBPK model, validated using preclinical data, can be used to estimate clinical local exposure levels of aflibercept (AFL), a biologic therapy used in treating Neovascular Age-Related Macular Degeneration.



Figure 1: OCAT model schematic

PBPK models can predict biologic drug's ocular exposure in humans following intravitreal administration.

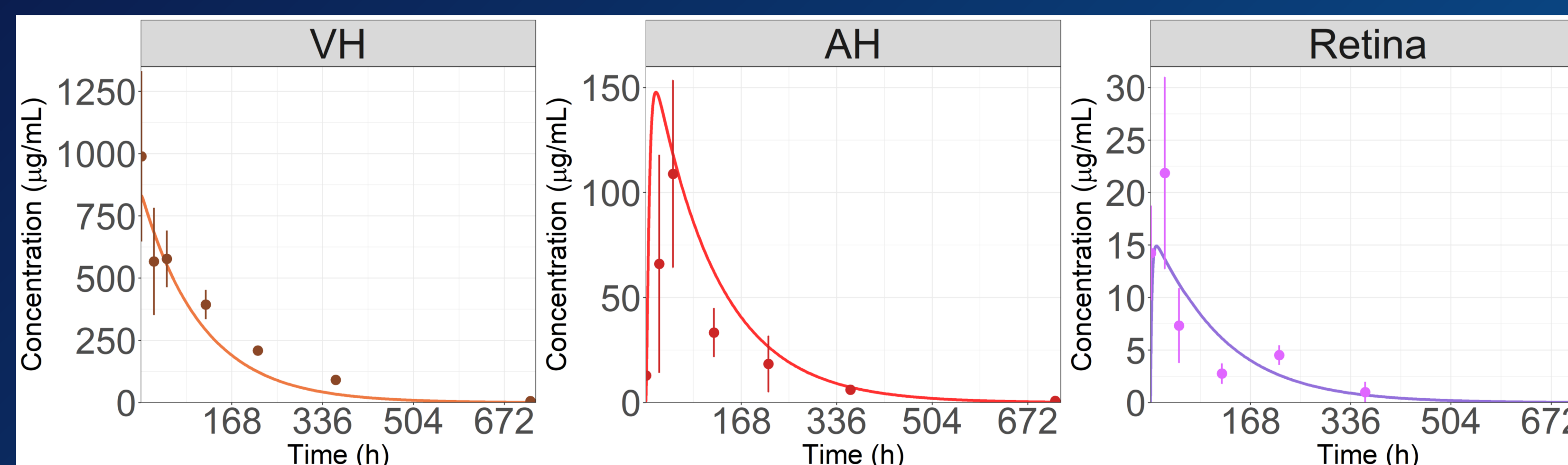


Figure 2: Observed (dots) and simulated (lines) aflibercept aqueous humor, vitreous humor, and retina concentrations in rabbits following intravitreal administration.

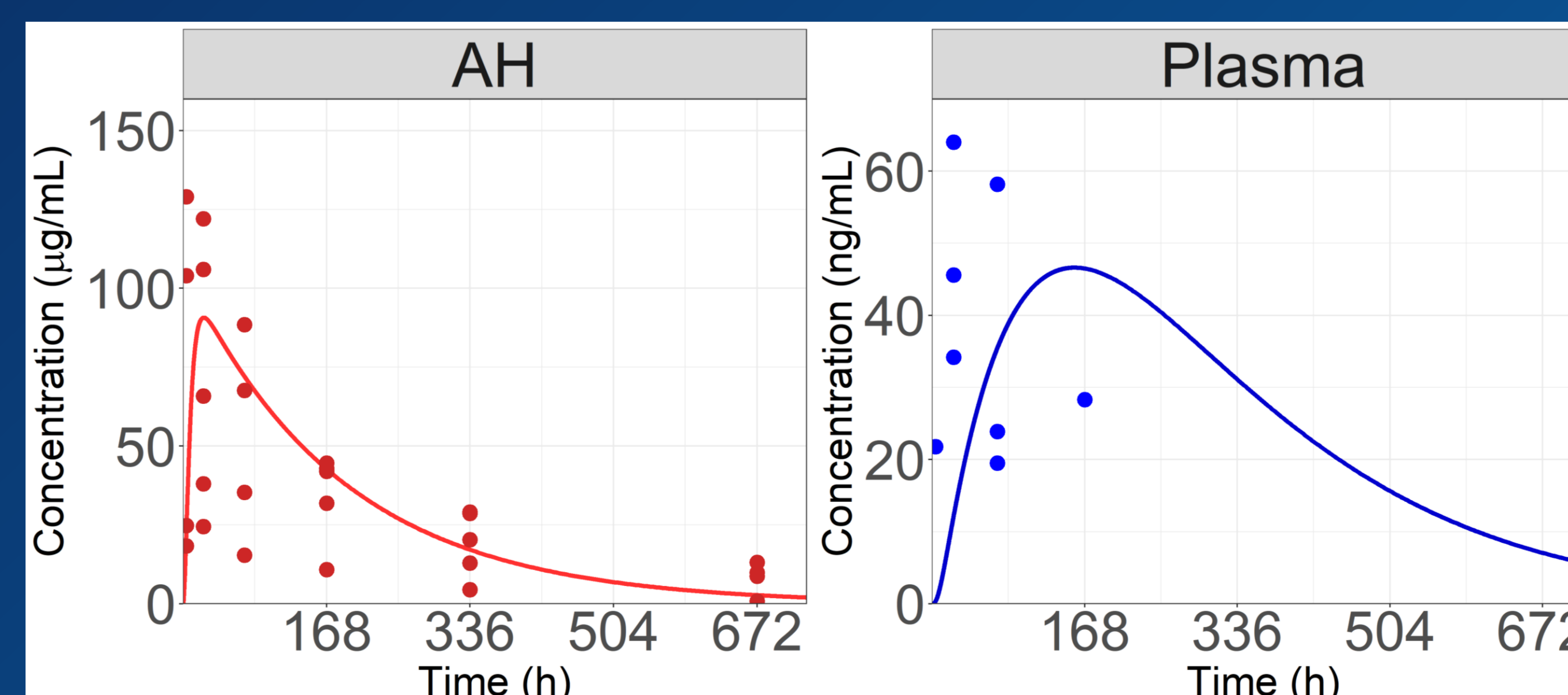


Figure 3: Observed (dots) and simulated (lines) aflibercept plasma and aqueous humor concentrations in humans following intravitreal administration.

METHODS

- AFL's systemic distribution and elimination, were based on its reported volume of distribution (6 liters) and elimination half-life.
- The OCAT™ model within GastroPlus® v9.9 was then used to build AFL O-PBPK model.
- After validation in rabbits, the O-PBPK model was applied to predict AFL pharmacokinetics in humans, with only physiological parameters modified to reflect human anatomy.

RESULTS

- The OCAT model successfully described the observed AFL aqueous humor, vitreous humor, and retina concentrations in rabbits following intravitreal administration (Figure 2).
- Adjusting the physiological parameters of the OCAT model to describe the human eye allowed for a reasonable prediction of AFL clinical systemic and ocular exposures following its intravitreal administration (Figure 3).

CONCLUSIONS

- This case study demonstrates the potential of a mechanistic, model-based preclinical-to-clinical translation approach to predict both local and systemic exposure of a biologic drug in humans following its intravitreal administration.
- This methodology could significantly influence the development of both novel and generic biologic ophthalmic drug products.

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