Predicting Brinzolamide Ocular Response in Humans Using an Ocular PBPK-PD Modeling and Simulation

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PURPOSE

- The development of generic ophthalmic drug products indicated for intraocular pressure (IOP) reduction typically relies on comparative pharmacodynamic (PD) endpoint bioequivalence (BE) studies.
- These studies present challenges for the pharmaceutical industry due to their high costs and limited sensitivity to formulation differences.
- More efficient BE methods are needed to support the development of generic IOP-reducing drug products.
- Ocular physiologically based pharmacokinetic (O-PBPK) modeling is an alternative to support BE assessment of generic ophthalmic drug products.
- There is an increasing number of case studies of O-PBPK models predicting clinical pharmacokinetics (PK) for ophthalmic drug products.
- Brinzolamide (BRI) is a first-line medication for IOP diseases.

OBJECTIVES

- Predict ocular PKs and PDs in rabbits following topical administration of BRI suspension (Azopt®)
- Predict ocular PD response in humans following topical administration of BRI suspension (Azopt®)

METHODS

- All simulations were performed using GastroPlus® (Version 9.9 Simulation Plus Inc., Research Triangle Park, NC, USA). The Ocular Compartmental Absorption and Transit (OCAT™) model was used to build an O-PBPK model for BRI suspension. The OCAT accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye. The PDPlus™ module within GastroPlus was then employed to model the effect of BRI on IOP.
- The O-PBPK model was initially validated using rabbit PK data following BRI topical suspension administration. The PD model describing BRI IOP reduction was validated using rabbit data.
- The O-PBPK-PD model was subsequently applied to predict the observed PD in humans, with physiological parameters adjusted to reflect human physiology. All drug-specific PK and PD parameters, along with their associated variability, were maintained consistent across species.

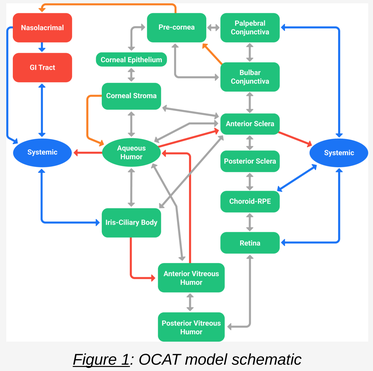

Figure 1: OCAT model schematic

RESULTS

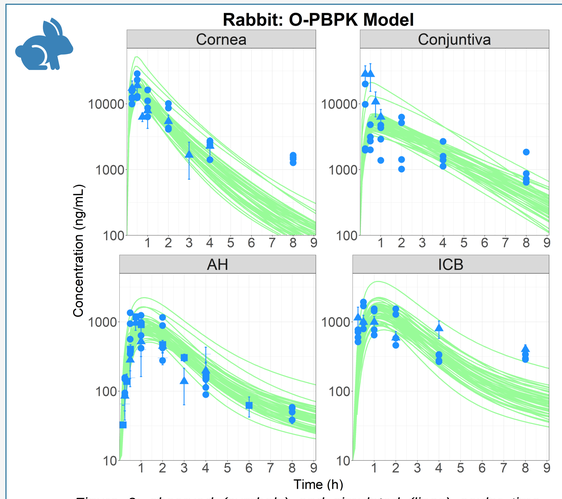

Figure 2: observed (symbols) and simulated (lines) ocular time courses in NZ rabbits following a single administration of BRI suspension 1%. Abbreviations: NZ: New Zealand; AH: Aqueous Humor; ICB: Iris-ciliary body.

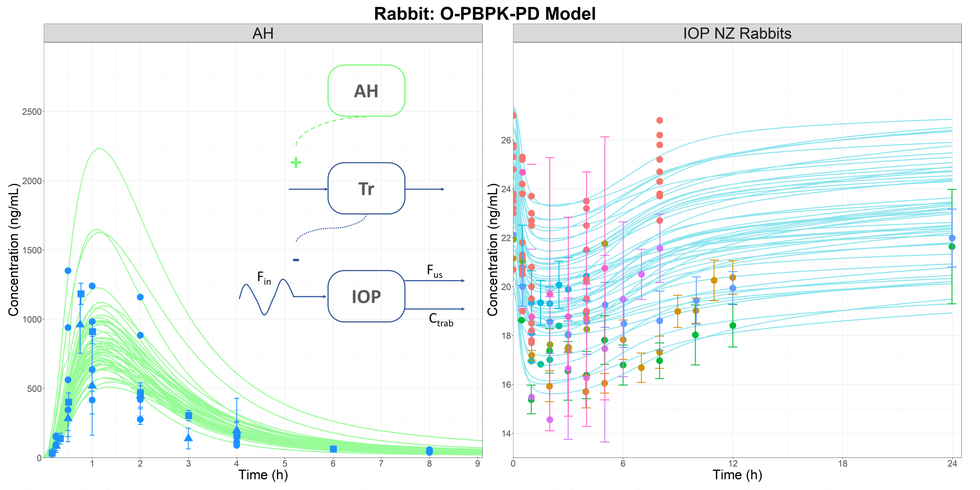

Figure 3: Observed (circles) and simulated (lines) AH concentrations (left) and IOP (right) in NZ rabbits following a single administration of Azopt 1%. The indirect IOP PD model structure is also presented. Abbreviations: NZ: New Zealand; AH: Aqueous Humor; Tr: Transit Compartment; IOP: Intraocular Pressure F_{in}: AH Inflow; F_{us}: AH Uveoscleral Outflow; C_{trab}: AH Trabecular Meshwork Outflow.

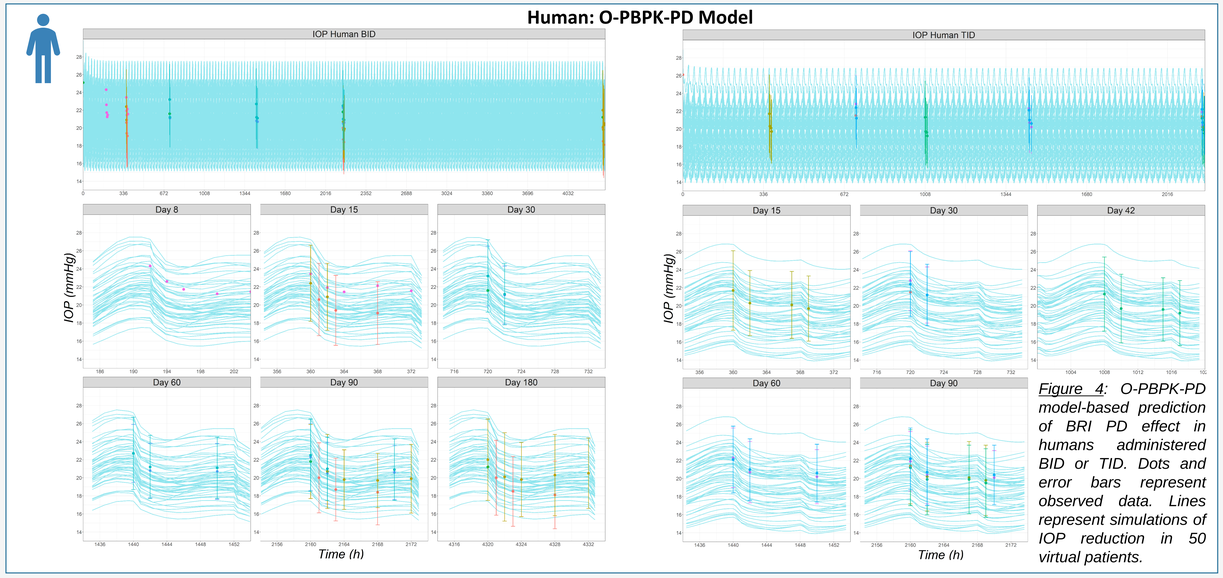

Figure 4: O-PBPK-PD model-based prediction of BRI PD effect in humans administered BID or TID. Dots and error bars represent observed data. Lines represent simulations of IOP reduction in 50 virtual patients.

CONCLUSION

- This case study demonstrates the O-PBPK-PD model's capability to describe IOP reduction following BRI administration in rabbits.
- It highlights the model's ability to predict the PD effect in humans using a mechanistic, model-based preclinical-to-clinical translation approach.
- This methodology could support the development of both new and generic ophthalmic drug products by defining a design space for these products.

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