Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Besifloxacin Suspension Case Study

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PURPOSE

- Development of generic ophthalmic drug products is challenging due to the complexity of the ocular system and a lack of sensitive testing tools to evaluate its interplay with ophthalmic formulations
- Due to their poor sensitivity, and associated costs, comparative clinical endpoint bioequivalence (BE) studies for a generic ocular drug product are a significant challenge to the pharmaceutical industry
- Ocular physiologically based pharmacokinetic (O-PBPK) modeling is an alternative to support regulatory assessment of ophthalmic drug products
- O-PBPK models have already demonstrated their value to predict clinical pharmacokinetics (PK) for ophthalmic solutions[1]
- The purpose of this research is to demonstrate the ability of O-PBPK models, validated against rabbit PK data, to predict clinical ocular exposure, following topical administration of ophthalmic suspensions

OBJECTIVES

- Validate an O-PBPK model for besifloxacin (Bes) administered as an ophthalmic suspension in rabbits
- Predict Bes clinical ocular exposure following topical administration in healthy subjects and patients undergoing cataract surgery

METHODS

- All simulations were performed using GastroPlus® version 9.8.3 (Simulation Plus Inc., Lancaster, CA, USA)
- Ocular Compartmental Absorption and Transit (OCAT™) model was used to build an O-PBPK for Bes ophthalmic suspension (Besivance® 0.6%). The OCAT accounts for tear drainage, ocular absorption, and distribution
- Besivance was modeled as a control release formulation due to the presence of Durasite ® in the formulation
- Cornea epithelium and conjunctiva permeabilities, and iris ciliary body systemic absorption rate were optimized to capture rabbit data. Bes release profile was also fitted
- External validations were performed using three additional ocular PK datasets in rabbits
- The OCAT model was subsequently used to predict Bes exposure in humans by adjusting the physiological parameters to match human ocular physiology. All of Bes specific parameters, including the release rate, were kept constant between rabbit and human simulations

RESULTS

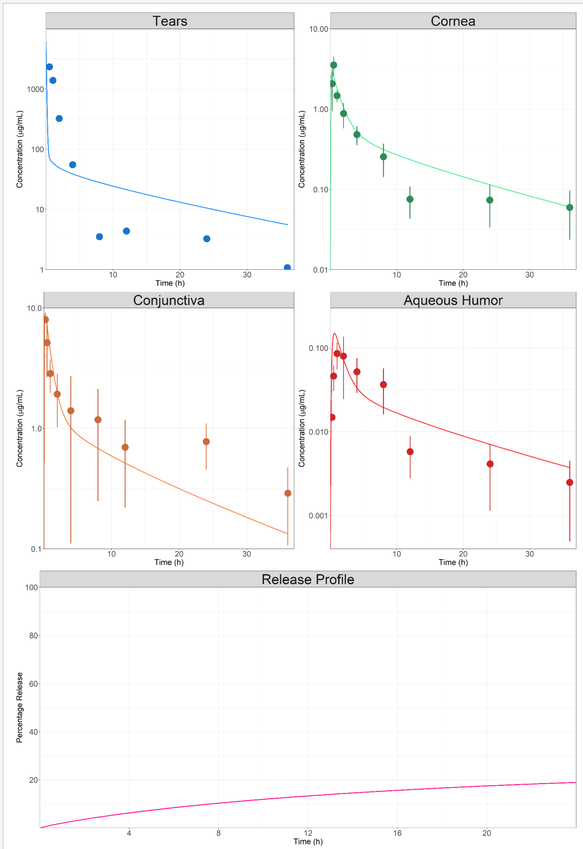

Figure 1: OCAT model development in New Zealand rabbits: Top and Middle rows: concentration time course following the unilateral administration of Bes suspension in a rabbit eye[2]. Bottom row: fitted release profile for Besivance 0.6 %. Circles are observed data and lines are simulated concentrations.

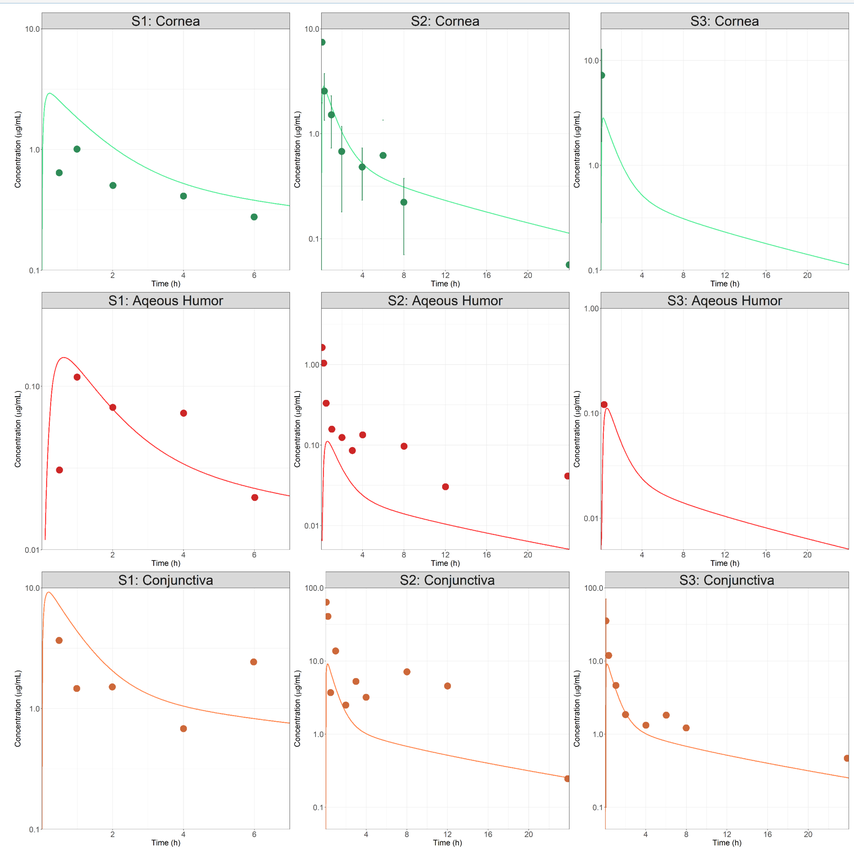

Figure 2: OCAT model validation: cornea (top row), aqueous humor (middle row), and conjunctiva (bottom row) concentration-time courses following the single administration of Bes suspension 0.6 % in New Zealand rabbits[3] (S1) and Dutch Belted rabbits[4,5] (S2 & S3)

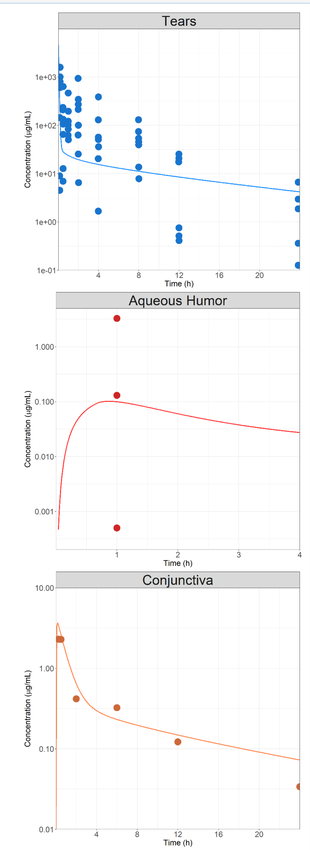

Figure 3: Human extrapolation for healthy subjects[4,6] and patients[7] undergoing cataract surgery receiving a single administration of Besivance 0.6 %.

CONCLUSION

- Preliminary data suggest that the OCAT model reasonably predicts human ocular exposure once validated with rabbit ocular PK data for Bes ophthalmic suspension
- The model reasonably predicts observations sampled from healthy subjects and patients undergoing cataract surgery
- Due to the significant intersubject and interstudy variability in observed human ocular exposure, extrapolation from more case studies is necessary to validate the O-PBPK extrapolation method
- Successful clinical extrapolation of Bes ophthalmic suspension represents an important step in validating the use of O-PBPK models for the prediction of human ocular exposure following topical administration of ophthalmic suspension drug products

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