W1230-02-10

Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Gatifloxacin Solution Case Study

Farah Al Qaraghuli[1], Ming-Liang Tan[2], Ross Walenga[2], Andrew Babiskin[2], Liang Zhao[2], Viera Lukacova[1] and Maxime Le Merdy[1]

1: Simulations Plus, Inc. Lancaster, CA. USA
2: Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD. USA

CONTACT INFORMATION: farah.alqaraghuli@simulations-plus.com

aaps PharmSci 360

PURPOSE

- Development of generic ophthalmic drugs has been extremely challenging due to the complexity of the ocular system and a lack of sensitive testing tools to evaluate its interplay with ophthalmic formulations.
- Identifying the impact of formulation, manufacturing, and physicochemical properties between a generic ocular drug product and its reference listed drug product is critical to maintain safety and efficacy.
- Conducting comparative clinical endpoint bioequivalence (BE) studies for generic ocular drug products is a significant challenge to pharmaceutical industry due to their associated cost and poor sensitivity.
- FDA is supporting ongoing efforts for the development of generic ophthalmic drug products and the enhancement of ocular PBPK modeling to support alternative BE approaches.
- The purpose of this research is to demonstrate the value of ocular mechanistic absorption models linked to physiologically based pharmacokinetic (PBPK) models validated against rabbit pharmacokinetic (PK) data to predict clinical ocular exposure.
- Enhancement of PBPK modeling is crucial in supporting an alternative BE approach where rabbits are the preferred animal species for PBPK-based extrapolation to predict exposure in human ocular tissue due to the physiological similarities between the rabbit and human eyeballs.

OBJECTIVES

- Develop and validate a PBPK model for gatifloxacin (Gat) administered as an ophthalmic solution in rabbits.
- Predict Gat clinical ocular exposure following topical administration in healthy subjects and in patients undergoing cataract, vitrectomy, and keratoplasty surgeries.

METHODS

- All simulations were performed using GastroPlus® version 9.8.2 (Simulation Plus Inc., Lancaster, CA, USA).
- The Ocular Compartmental Absorption and Transit (OCAT™) model was used to build a PBPK for Gat ophthalmic solution. The model accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye.
- Cornea epithelium permeability and iris ciliary body (ICB) systemic absorption rate were optimized to capture rabbit data from two studies. External validations were performed using ten additional studies.
- The OCAT model was subsequently used to predict Gat exposure in humans by adjusting the physiological parameters to match human ocular physiology. All the Gat specific parameters were kept constant between rabbit and human simulations.

RESULTS

Preclinical studies used for Gat ophthalmic solution OCAT model development and validation in rabbit (Figure 1) were based on single or multiple dose administrations of 0.3% (w/v) Gat solution in New Zealand White (NZ), Japanese White (assumed to be similar to NZ), or Dutch Belted (DB) rabbits. The administered volumes were 50 µL in all studies except GA.NZ.4, where 40 µL was administered.

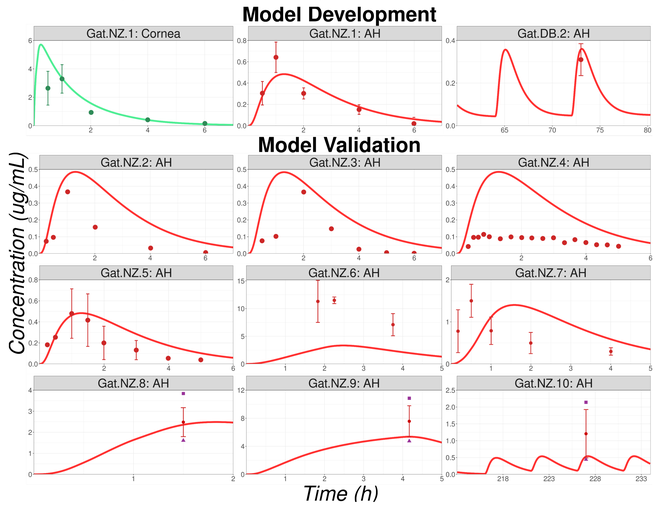

Figure 1: OCAT model development and validation in rabbit: Concentration-time courses in cornea (green) and aqueous humor (AH, red) following the unilateral administration of Gat solution in a rabbit eye. Symbols are observed data and lines are simulated concentration-time courses.

Clinical studies used for human extrapolation (Figures 2-5) were based on single or multiple dose administrations of 39 µL of 0.3% (w/v) Gat solution in healthy subjects (Figure 5) and in patients undergoing cataract surgery (Figure 2), keratoplasty (Figure 3), or vitrectomy (Figure 4).

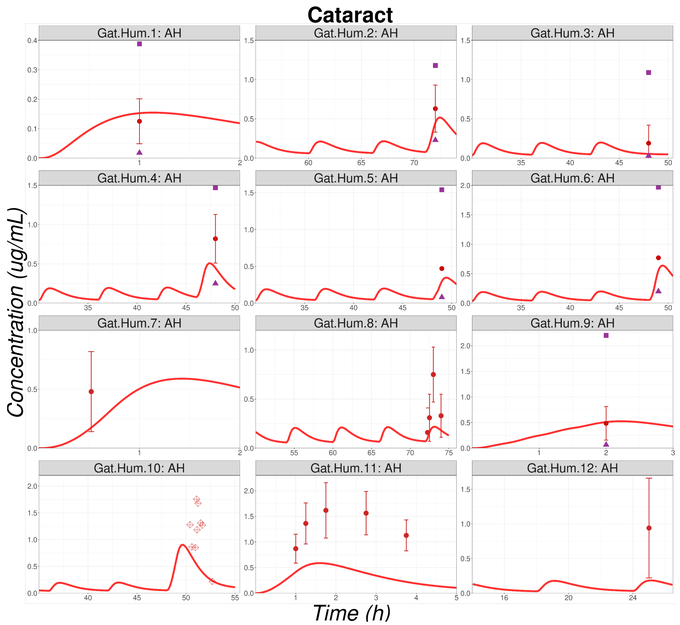

Figure 2: Human extrapolation: predicted AH profiles for patients undergoing cataract surgery. Circles are observed and lines are simulated concentration-time courses. Diamonds represent individual data points.

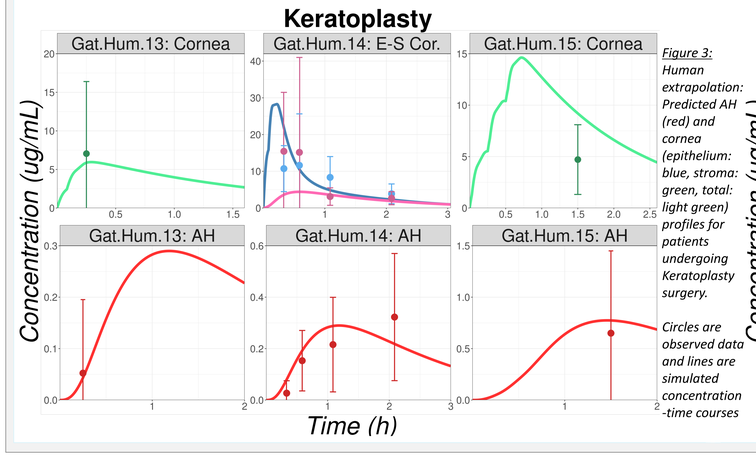

Figure 3: Human extrapolation: Predicted AH (red) and cornea (epithelium: blue, stroma: green, total: light green) profiles for patients undergoing Keratoplasty surgery.

Circles are observed data and lines are simulated concentration -time courses

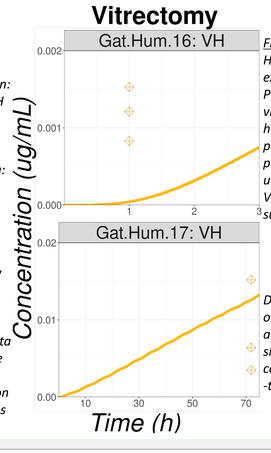

Figure 4: Human extrapolation: Predicted vitreous humor profiles for patients undergoing Virectomy surgery.

Diamonds are observed data and lines are simulated concentration -time courses.

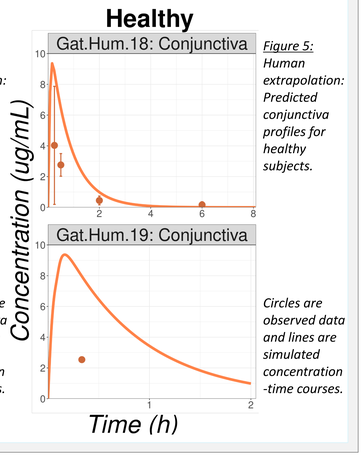

Figure 5: Human extrapolation: Predicted conjunctiva profiles for healthy subjects.

Circles are observed data and lines are simulated concentration -time courses.

CONCLUSIONS

- The OCAT model provided a reasonable prediction of Gat ocular exposure in humans, once validated based on preclinical rabbit data.
- Validation of PBPK models using preclinical data helps support drug development, which potentially helps providing a better understanding of the impact of formulation modifications on the performance of ophthalmic solution products.
- The significant human intersubject and interstudy variability observed in all ocular tissues' exposures render the conclusion on extrapolation method using a PBPK model premature based solely on this case study. However, the successful clinical extrapolation of Gat solution, combined with results for other fluoroquinolones (data not shown), represents an important step in the validation process of the extrapolation method used to predict human ocular exposure for all ophthalmic drug products.
- This PBPK model extrapolation approach is expected to have a significant impact on ophthalmic generic drug product development.

FUNDING/GRANT

This project is funded by the U.S. Food and Drug Administration: grant number: 1U01FD006927.

Disclaimer: This poster reflects the views of the authors and should not be construed to represent the FDA's views or policies.

FDA U.S. FOOD & DRUG ADMINISTRATION

SimulationsPlus