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Clinical Ocular Exposure Extrapolation Using PBPK Modeling and Simulation: Levofloxacin Solution 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
- Identifying the impact of any differences in manufacturing, formulation, or physicochemical characteristics between a generic ocular drug product and its reference listed product is critical to maintain safety and efficacy for patients
- Due to their poor sensitivity, associated costs, and ethical limitations, comparative clinical endpoint bioequivalence (BE) studies for a generic ocular drug product are a significant challenge to pharmaceutical industry and a burden for generic development
- The purpose of this research is to demonstrate the value of ocular mechanistic absorption models (MAM) linked to physiologically based pharmacokinetic (PBPK) models validated against rabbit pharmacokinetic (PK) data to predict clinical ocular exposure

OBJECTIVES

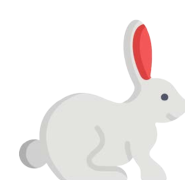
- To develop and validate a MAM-PBPK for levofloxacin (Lev) administered as an ophthalmic solution in rabbits
- To predict Lev clinical ocular exposure following topical administration in patients undergoing cataract, virectomy, keratoplasty, and corneal transplant surgeries

METHODS

- All simulations were performed using GastroPlus® (Version 9.8 Simulation Plus Inc., Lancaster, CA, USA)
- Ocular Compartmental Absorption and Transit (OCAT™) model was used to build a MAM for Lev ophthalmic solution. The OCAT accounts for nasolacrimal drainage, ocular absorption, and distribution in the eye
- Cornea epithelium and conjunctiva permeabilities were optimized to capture rabbit data. External validations were performed using five additional ocular PK datasets in rabbits
- The OCAT model was subsequently used to predict Lev exposure in humans by adjusting the physiological parameters to match human ocular physiology. All of Lev specific parameters were kept constant between rabbit and human simulations

RESULTS

Table 1: Summary of pre-clinical studies used for Lev solution OCAT model development and validation in rabbit



Study	Species	BW (kg)	Gender	Doses	Dose Frequency	Volume (µL)
A	Japanese White	2.25	both	1.50%	single	30
B	New Zealand	2.75	N/A	0.50%	4 times per 10min	50
C	New Zealand	2.5	female	1.50%	single	50
D	New Zealand	2.3	female	1.50%	single	50
E	New Zealand	2.75	male	0.50%	3 times per 15min	50
F	Dutch Belted	2	male	0.50%	single	50

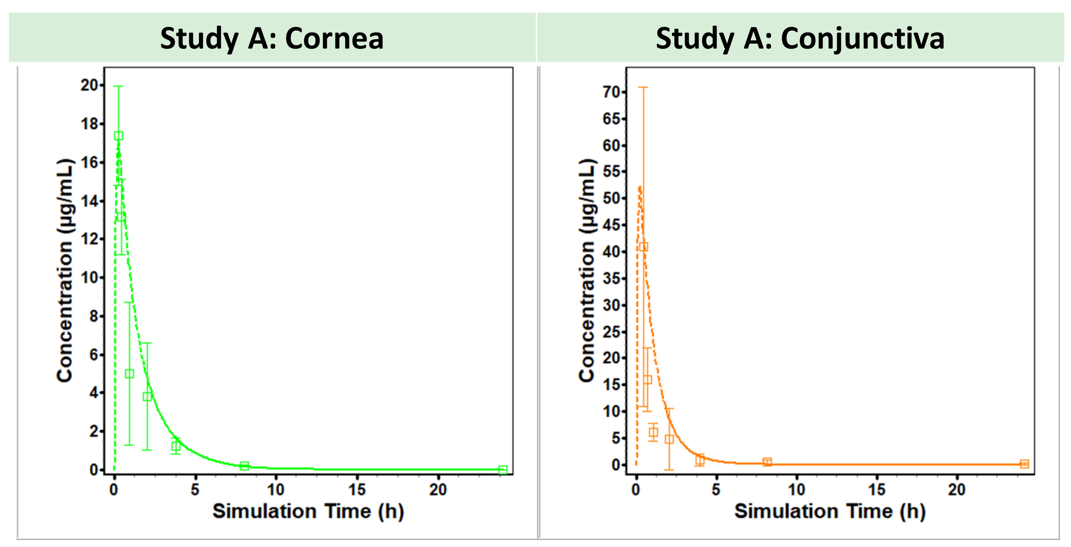


Figure 1: OCAT model development: Concentration-time course following the unilateral administration of 30 µL of Lev solution 1.5 % in a rabbit eye: (Study A). Data points are observed mean ± SD and lines are simulated concentration time courses.

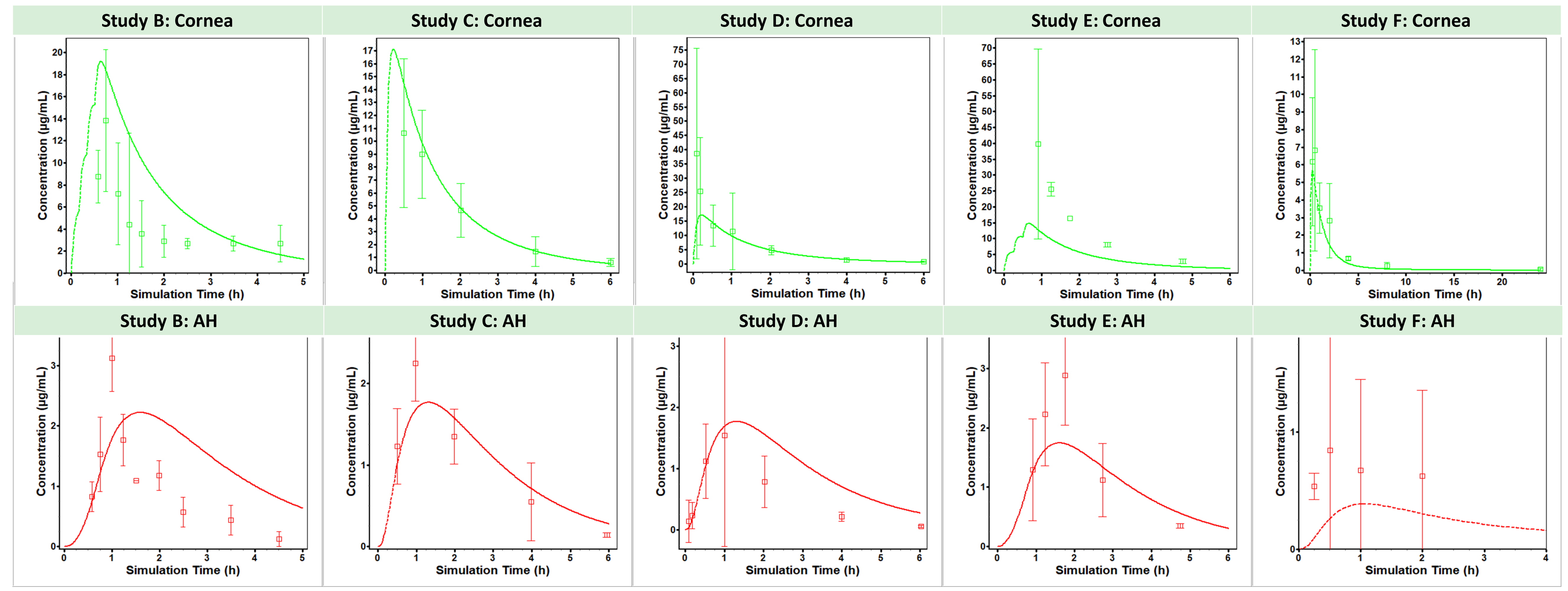


Figure 2: OCAT model validation: Concentration-time course following administration of Lev solution in a rabbit eye. Study designs are presented in Table 1: (Study B, C, D, E, F). AH: Aqueous humor. Data points are observed mean ± SD and lines are simulated concentration time courses.

Table 2: Summary of clinical studies used for human extrapolation to predict clinical ocular exposure following topical (solution) and PO Lev administration

Study	Surgery	Gender	ROA	Doses	Dose Frequency	Volume (µL)
A	Cataract	M&F	Topical	0.5%	15, 30, 45, 60 min before surgery	39
B	Cataract	M&F	Topical	0.5%	15, 30, 45, 60 min before surgery	39
C	Cataract	M&F	Topical	0.5%	60, 75, 90 min before surgery	39
D	keratoplasty	M&F	Topical	0.5%	60, 75, 90 min before surgery	39
E	corneal transplant	M&F	Topical	1.5%	15, 10 min before surgery	39
F	keratoplasty	M&F	Topical	0.5%	60, 75, 90 min before surgery	39
G	Virectomy	M&F	Topical	0.5%	3 doses the day before surgery, 20, 40, 60, 80, 100, 120 min before surgery	39
H	Virectomy	M&F	PO	750 mg	-	-
I	Virectomy	M&F	PO	200 mg	3 doses the day before surgery, 180 min before surgery	-

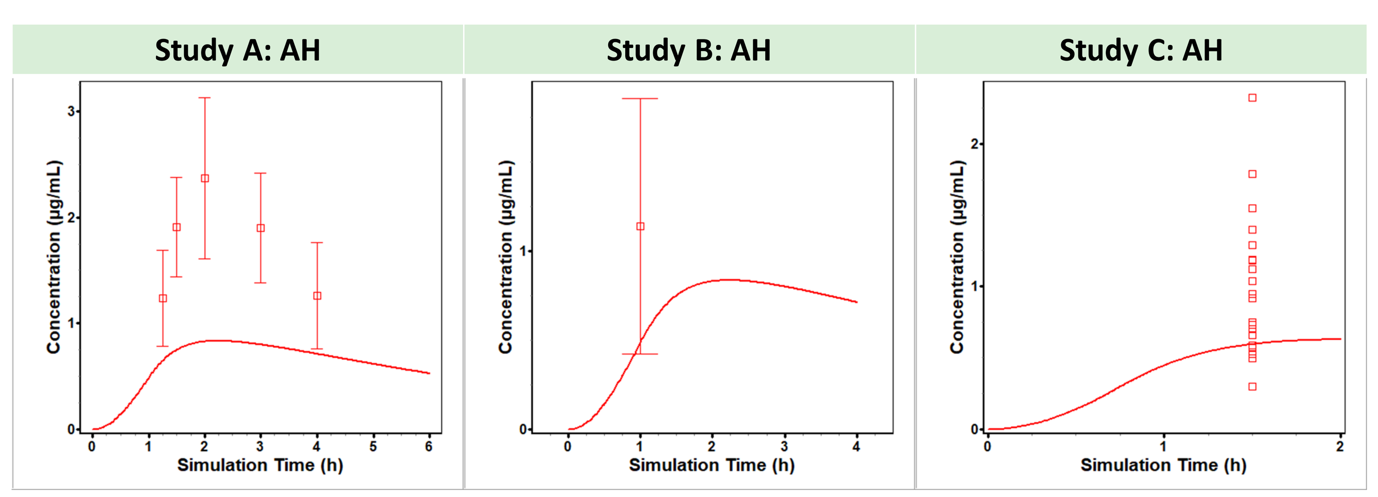


Figure 3: Human extrapolation for patients undergoing cataract surgery: Concentration-time course following the unilateral administration of 39 µL of Lev solution 0.5 % in patients (Study A, B, C). Data points are observed mean ± SD and lines are simulated concentration time courses.

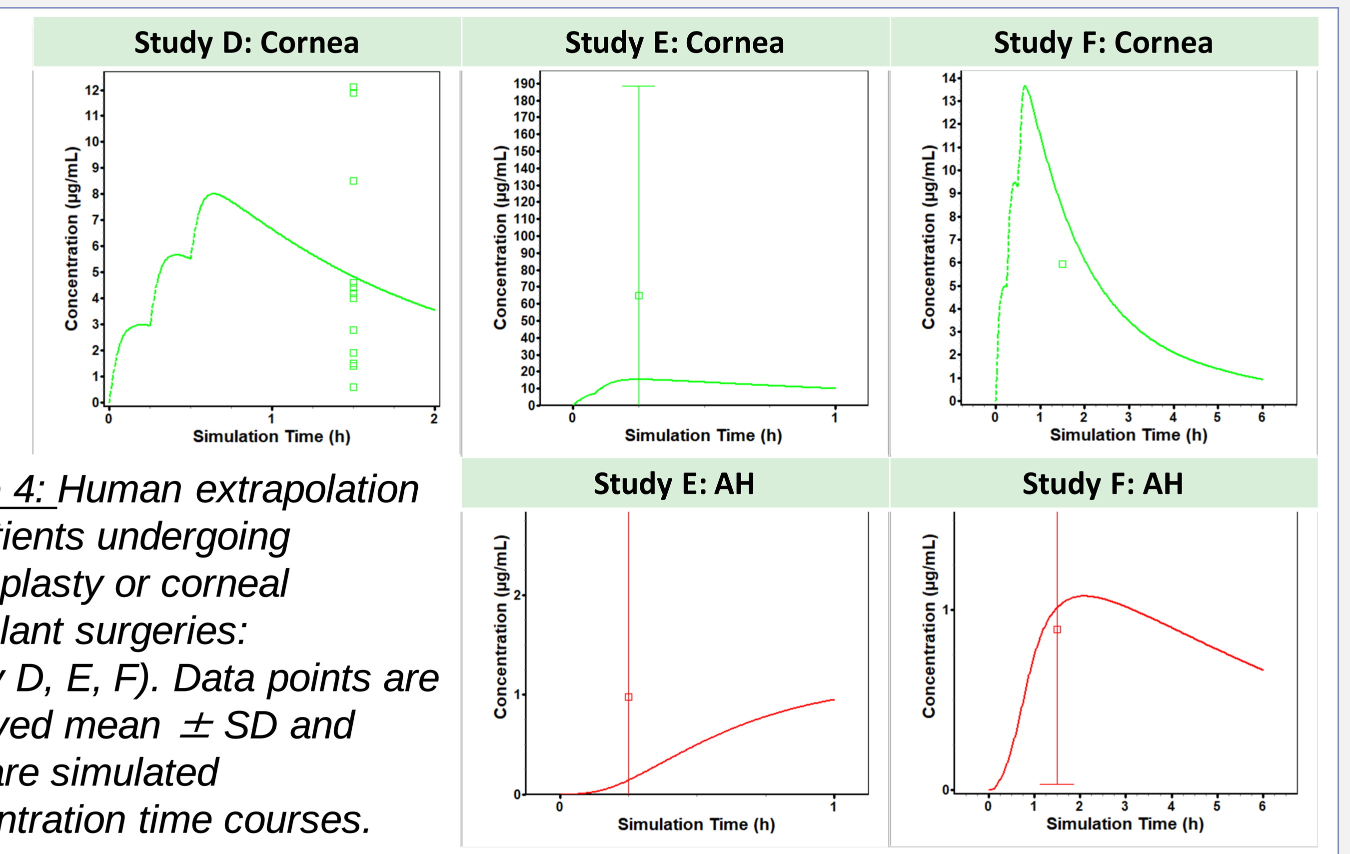


Figure 4: Human extrapolation for patients undergoing keratoplasty or corneal transplant surgeries: (Study D, E, F). Data points are observed mean ± SD and lines are simulated concentration time courses.

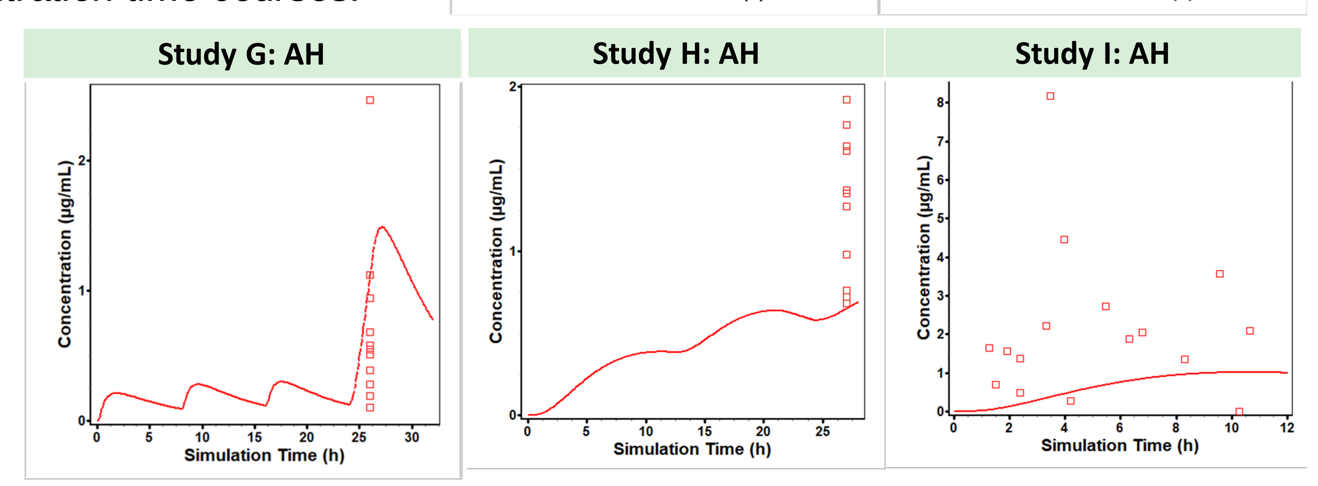


Figure 5: Human extrapolation for patients undergoing virectomy surgery following topical (Study G) or PO administrations (Study H, I). Data points are observed mean ± SD and lines are simulated concentration time courses.

CONCLUSIONS

- Preliminary data suggest that the OCAT model reasonably predicts human ocular exposure once validated with rabbit ocular PK data for solutions
- The model reasonably predicts observations sampled from patients with cataract, virectomy, keratoplasty, and corneal transplant surgeries
- Due to the significant intersubject and interstudy variability in observed human ocular exposure, extrapolation from more case studies is necessary to validate the MAM-PBPK extrapolation method
- Successful clinical extrapolation of levofloxacin solution represents an important step in validating the use of MAM-PBPK models for prediction of human ocular exposure for ophthalmic drug products
- The approach described in this study is expected to have a significant impact on ophthalmic generic drug product development

FUNDING / GRANTS

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