

SIMULATION OF SYSTEMIC EXPOSURE AFTER MULTIPLE OCULAR ADMINISTRATION OF BILASTINE OPHTHALMIC SOLUTION FOR SAFETY ASSESSMENT IN CHILDREN

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INTRODUCTION

Bilastine is a non-sedating H1 antihistamine approved for treatment of allergic rhinoconjunctivitis and urticaria, at an oral dose of 20 mg once daily (OD) in adults and adolescents (≥12 years) and 10 mg OD in children <12 years. A bilastine 0.6% ophthalmic solution for allergic conjunctivitis (1 drop instilled in each eye OD) in adults and children aged ≥2 years is now under development.

OBJECTIVES

To simulate systemic PK levels arising from OD ocular administration of bilastine eye drops in children aged 2-<18 years, aimed at discarding associated safety issues. This is in accordance with the agreed paediatric investigation plan (PIP) [1], where a dedicated paediatric PK study was deemed irrelevant to the ophthalmic product performance.

METHODS

i. Modeling of PK data after ophthalmic bilastine in adults

Bilastine plasma concentration data in healthy adult volunteers (HVs) were obtained from two previous studies:

- Study BOFT-0318-PK (n=12 HVs receiving bilastine eye drops for 5 days)
- Study BILA-2909/BA [2] (n=12 HVs receiving a single 10 mg iv injection of bilastine).

Plasma levels from both studies were pooled and analysed in NONMEM v7.3 (FOCEI method) for estimation of pre-systemic popPK parameters characterising absorption of ophthalmic bilastine (absorption rate constant (Ka), relative bioavailability for the ocular route (F) and, if applicable, lag time (T_{lag})) as well as associated variabilities. No covariate analysis was carried out.

Goodness of fit diagnostic plots and visual predictive check (VPC) were used for model qualification.

ii. Simulation of ophthalmic bilastine disposition in paediatrics and comparison against oral PK

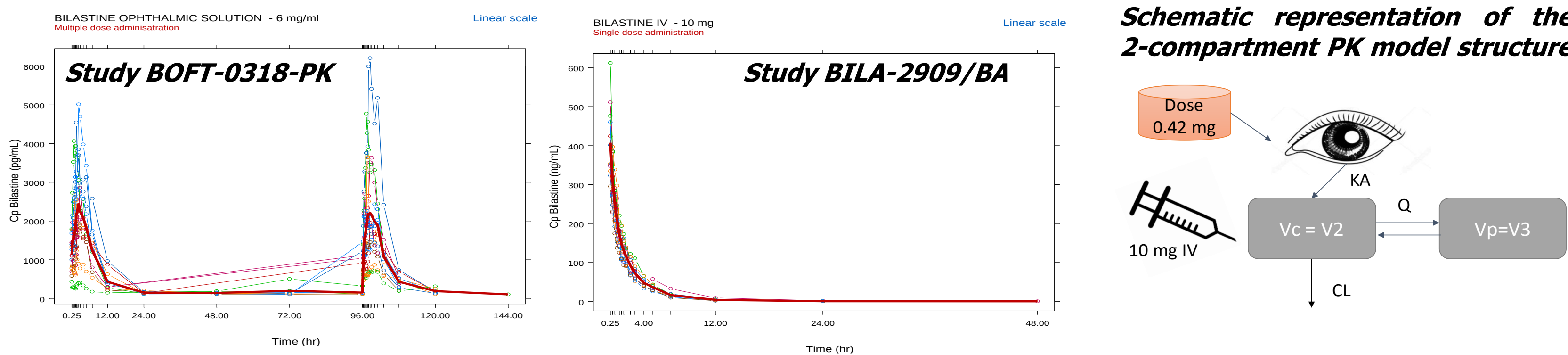
Estimated absorption kinetics of ophthalmic bilastine were assumed unchanged in the target paediatric population, in whom eye dimensions and pre-corneal factors are mostly like in the adult [3,4] (Scenario 1). However, two additional hypothetical (worst-case) scenarios were also explored via sensitivity analysis on the adult pre-systemic PK parameter values (Scenario 2: F increased by 30% + Ka increased by 30%; Scenario 3: F=100% + Ka increased by 30%).

Systemic PK parameters (and associated variabilities) from the paediatric popPK model previously developed for oral bilastine [5] were used in simulation instead of those estimated in adults above, under the assumption that systemic disposition is independent of the route of administration. The paediatric popPK model is deemed applicable in children aged ≥2 years given that all physiological processes involved in the disposition of the drug are fully mature by this age [5].

For each scenario, 500 Montecarlo datasets were simulated for ophthalmic bilastine after 28 days of ocular treatment (i.e., long-term exposure) in the paediatric population, and the 95% confidence interval of simulated individual plasma PK profiles was graphically overlapped, as a measure of safety threshold, with paediatric PK observations after repeated oral administration of bilastine 10 mg/day (study BILA-3009/PED, n=31), proven to be well tolerated in children aged ≥2 years (study BILA-3312/PED [6]). Graphics were performed using S-PLUS v8.

RESULTS

A two-compartment disposition model (same structure as for oral bilastine PK in adults and children) [5] with a single first-order Ka, no T_{lag} and proportional residual error best described pooled observations from both ocular and iv administration routes.



The relative bioavailability (F1 function) for the extravascular form was $F1 = 1 - \left(\frac{1}{1 + \text{Frac}} \right)$ while it was set to F1=1 for the iv route of administration

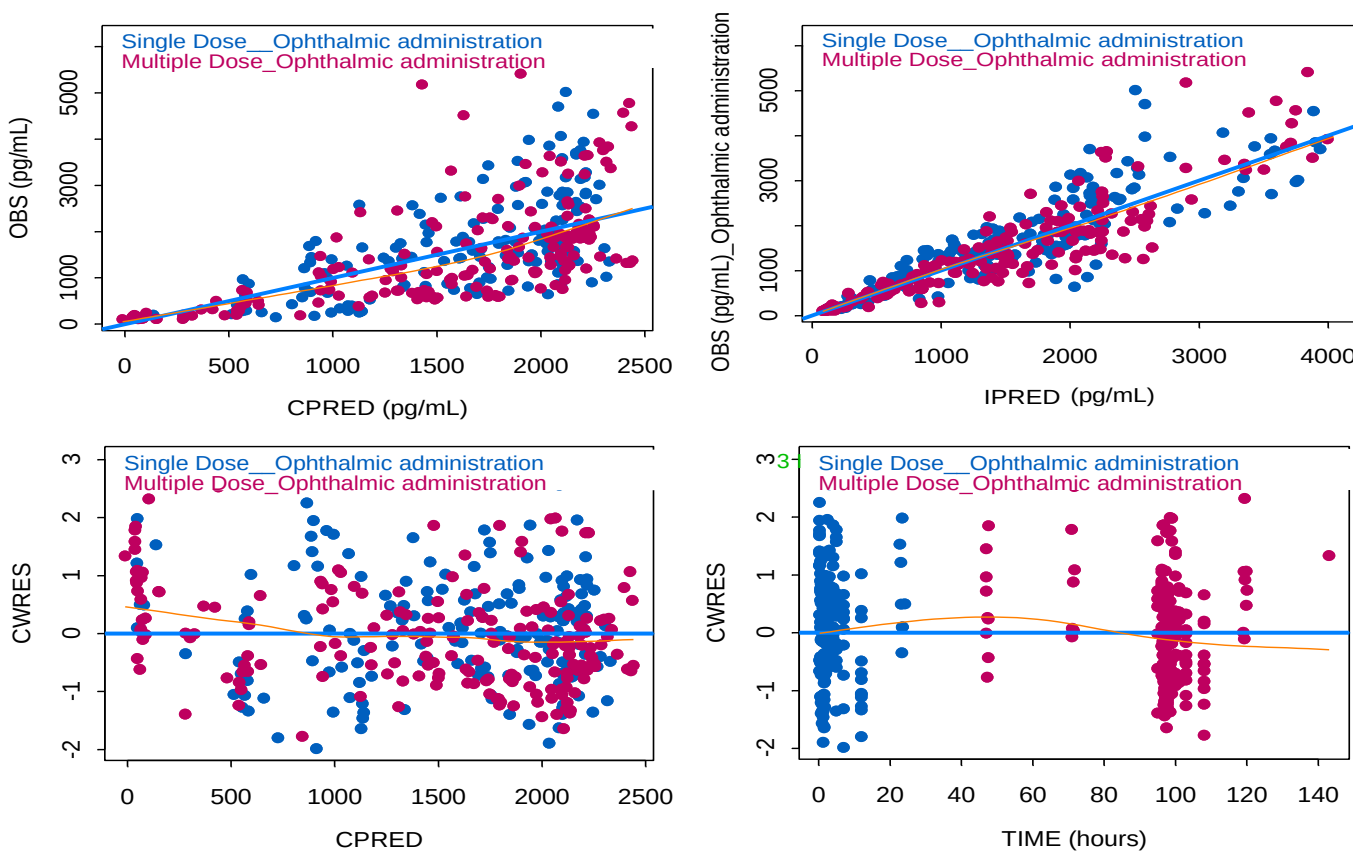
All structural parameters were well estimated (SEE<50%). The interindividual variability (modelled as exponential) was significant for all of them except volume of central compartment. Typical values of absorption-related parameters were F=59% and Ka=0.345 1/h.

Selected PK model predicts adequately bilastine disposition after repeated ophthalmic administration.

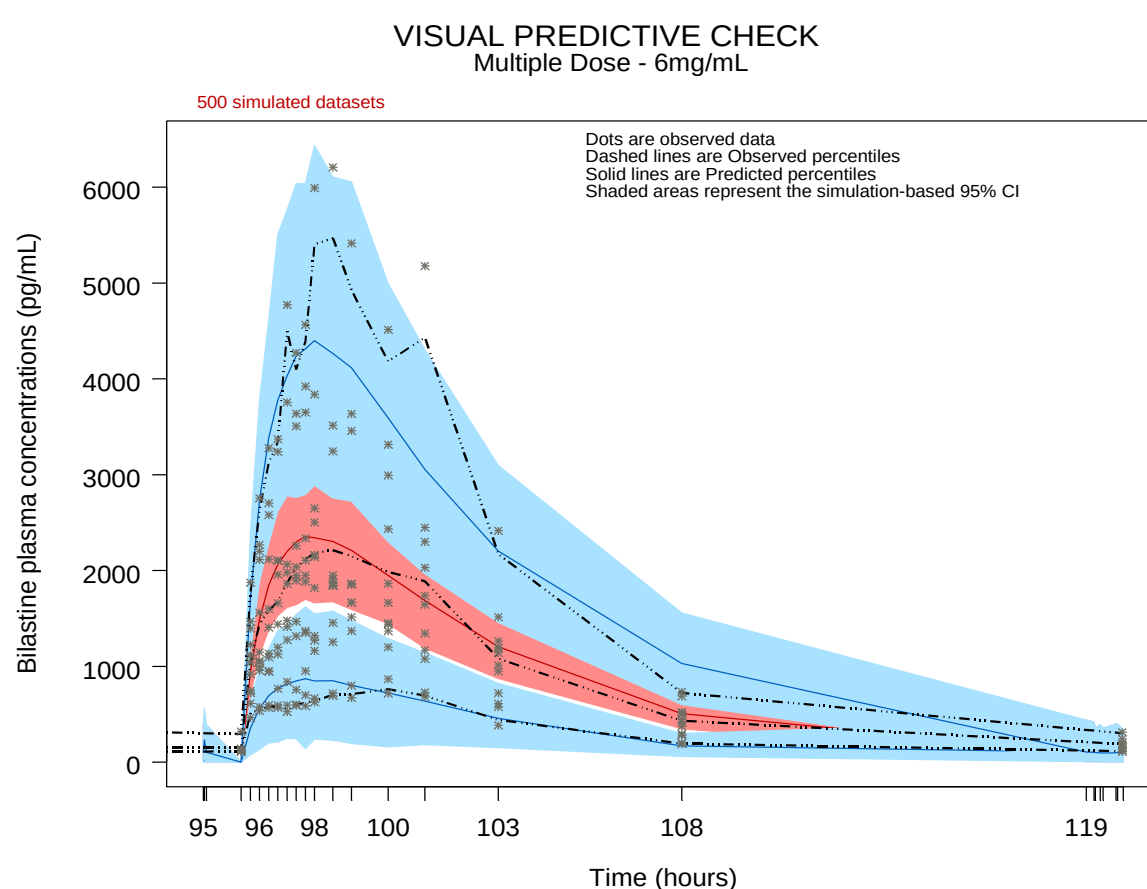
PopPK parameter estimates for ocular bilastine in adults

Parameter	Estimate	SEE (%)
CL (L/h)	12.6	5.1
V2 (L)	19.5	7.3
Q (L/h)	15.9	28.3
V3 (L)	31.7	18.8
Ka (1/h)	0.345	11.3
Frac	1.45	31.2
ω CL	14.5%	41.5
ω Q	97.3%	46.5
ω V3	82.1%	47.5
ω Ka	11.3%	189
ω Frac	77.2%	41.6
σ	33.6%	12.7

Goodness of fit plots for ophthalmic bilastine



VPC for ophthalmic bilastine



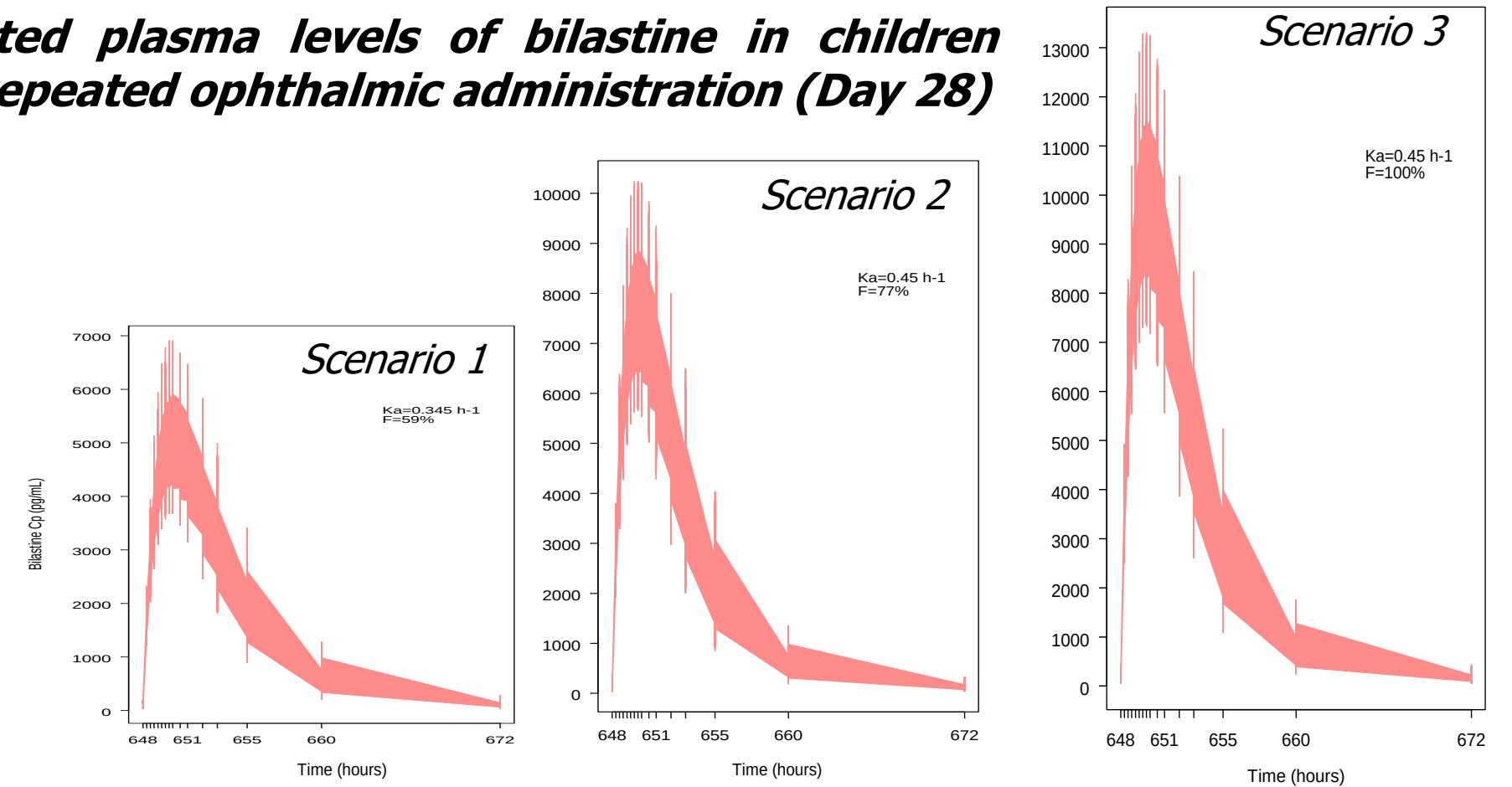
Simulated plasma levels of bilastine based on the PK parameters characterising absorption of ophthalmic bilastine as estimated in the adult (i.e., Ka=0.345 1/h and F=0.59) [Scenario 1] as well as according to the two additionally proposed worst-case scenarios are depicted below.

Simulations included inter-individual variabilities in Ka (as estimated in the adult) and CL (as estimated in children) as well as residual variability (from children) in order to construct confidence intervals.

Predicted plasma levels of bilastine in children after repeated ophthalmic administration (Day 28)

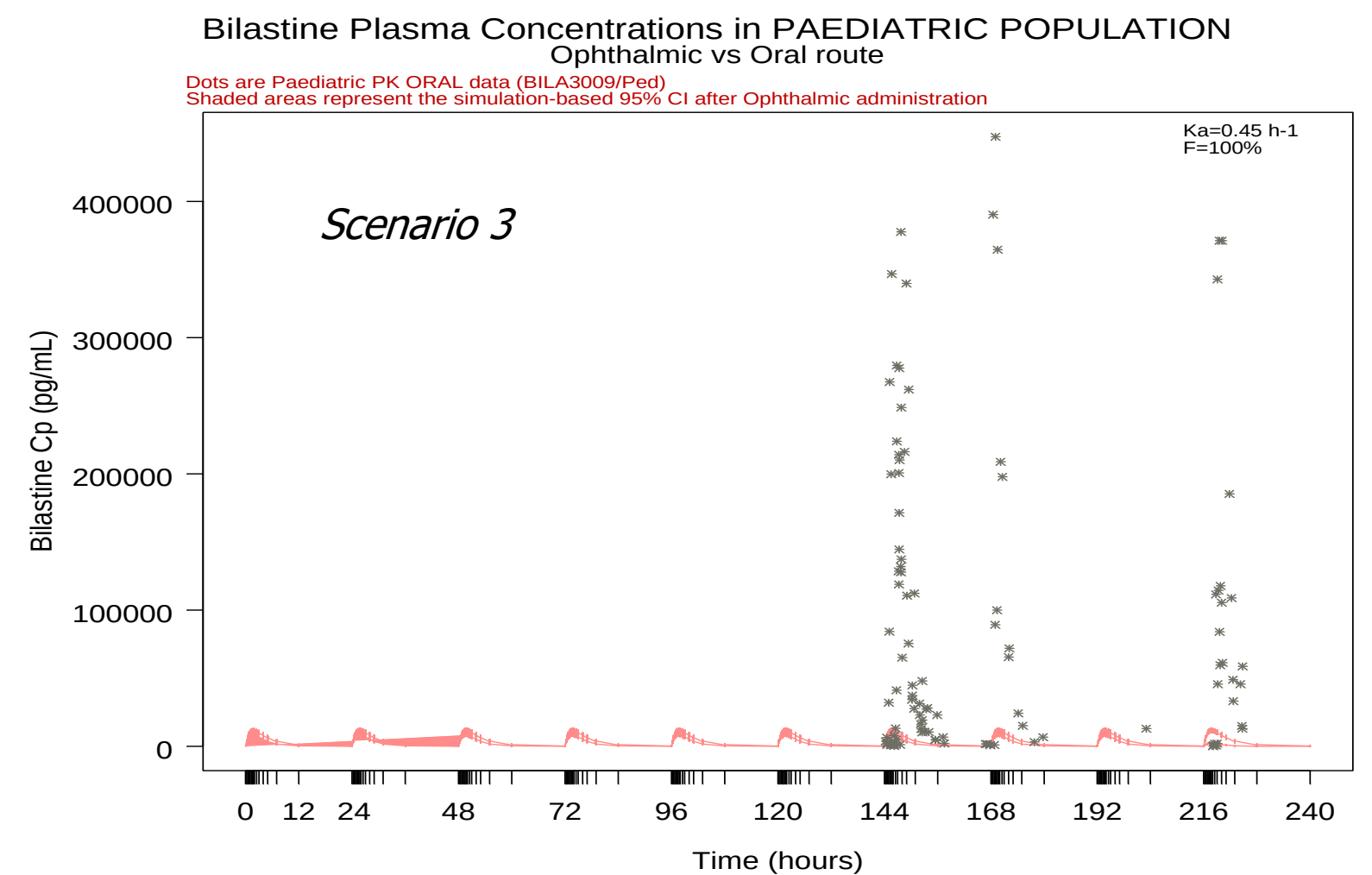
PopPK parameter estimates for oral bilastine in children

MODEL: bila-ped.all.4.3.1.4.1st OBJ: 597.7			
Parameter	Estimate	SEE	SEE%
KA (L/hr)	1.29	0.286	22.2
CL (L/hr)	12.5	0.74	5.9
V2 (L)	19.7	2.55	12.8
Q (L/hr)	2.01	0.684	34
V3 (L)	17.4	2.56	14.6
Tlag (hr)	0.183	0.0079	4.3
ω CL	15%	9%	40%
ω Ka	67%	37%	30%
σ	35%	17%	22%



In all three simulated Scenarios, the expected systemic exposure of bilastine after repeated ocular administration in children was far below that observed in the same population after oral bilastine 10 mg/day (pre-established threshold of safety).

Worst-case Scenario 3 is shown.



CONCLUSION

The absorption kinetics estimated for bilastine 0.6% ophthalmic solution in adults were used, in conjunction with the well-known systemic PK parameters of oral bilastine in children, to simulate plasma concentrations following multiple dosing of bilastine eye drops in the target paediatric population. Plasma levels attained through the ocular route were proven to be negligible in comparison with the systemic exposure corresponding to the therapeutic paediatric oral dose (10 mg/day), thus allowing to discard safety concerns without the need to conduct paediatric PK studies after ophthalmic administration of bilastine.

REFERENCES

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