

Bridging population pharmacokinetic and physiologically based pharmacokinetic approaches to evaluate APX3330 disposition



PRESENTER:
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BACKGROUND

APX3330 is an orally administered inhibitor of APE1/REF-1 with anti-angiogenic, anti-inflammatory and antineoplastic activities. This first-in-class drug has been studied for different applications including diabetic retinopathy and macular edema.

AIM: to compare population (PopPK) and physiological-based pharmacokinetic (PBPK) modeling approaches to describe the pharmacokinetic properties of APX3330.

METHODS

- APX3330 plasma concentration-time profiles were digitized from regulatory reports using WebPlotDigitizer 4.4.
- The PopPK analysis was conducted using Phoenix-NLME 8.0. FOCE-ELS was used to estimate structural parameters, and random effects. Covariates evaluated were weight, dose, and administration without vs. with a meal.
- The PBPK model was developed using GastroPlus 9.6 based on in silico predictions from ADMET Predictor 9.5. PBPK simulations were considered adequate if the mean fold error was within 2-fold.

PopPK and PBPK models provided similar predictions of PK parameters and the effect of food on the rate of absorption of APX3330 in healthy subjects.

Table 1. Pharmacokinetic parameters

	PopPK	PBPK
CL/F (mL/h)	205.6 ± 19.4	193.8 ± 11.84
V _{ss} /F (L)	9.2 ± 18.2	7.2 ± 17.2
ka (1/h) fasted	0.71 ± 20.3	0.65 ± 6.64
ka (1/h) fed	0.42 ± 14.1	0.36 ± 4.75
t _{max} (h) fasted	3.8	3.7
t _{max} (h) fed	5.4	5

RESULTS

- The PopPK of APX3330 was adequately described by a two-compartment model with first-order absorption. Inclusion of meal as a covariate on k_a improved the model fit.
- A full PBPK model was developed to describe APX3330 distribution. The V_{ss}/F and the Kp were predicted using the Lukacova method.
- Both modeling approaches show the co-administration of APX3330 with food prolonged absorption.

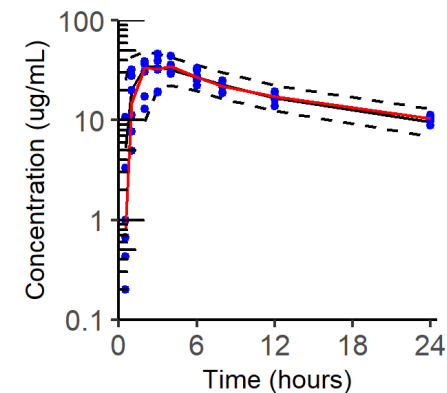


Fig 1. APX3330 plasma concentration profile predicted by PopPK. The median of observed concentrations (red line and blue circles), and median predicted (black solid line) and associated 5% and 95% limits of the 90% confidence interval (black dashed lines).

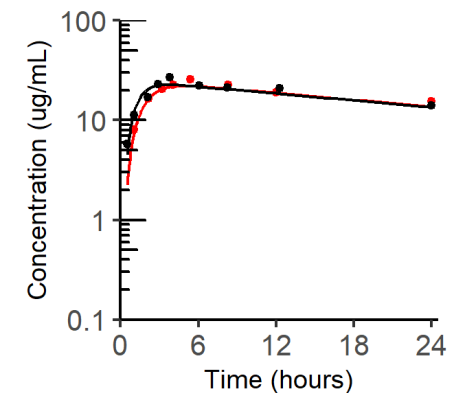


Fig 2. APX3330 plasma concentration profile predicted by PBPK model. The black line represents the fasted state and the red line the fed state. The circles represent the mean observed concentrations.



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