

Integration of a deconvolution approach in an abemaciclib parent-metabolite joint pharmacokinetic model

MANCHESTER
1824

The University of Manchester

Frédéric Lusoli¹, Céline Pitou², Leon Aarons¹ and Kayode Ogungbenro¹
¹ Centre for Applied Pharmacokinetic Research, University of Manchester, UK
² Global PK/PD & Pharmacometrics, Eli Lilly and Company, Bracknell, UK

Objectives

- To use a deconvolution approach on phase I abemaciclib data to describe absorption
- To develop a joint population pharmacokinetic (PopPK) model for abemaciclib and its active metabolite

Conclusions

- The abemaciclib parent-metabolites PopPK model described the plasma concentrations observed in healthy participants after a single oral 200mg dose.
- The deconvolution information will be translated to a PBPK model to optimise the metabolites' exposure.

Materials & Methods

- Serial PK sample up to 192 hours postdose were collected with a total of 710 parent-metabolite plasma concentrations from 10 volunteers. The characteristics are summarised in **Table 1**.

Table 1: Characteristics from the PopPK analysis dataset

Source	NCT02327143
Description	Absolute bioavailability study
Population	Healthy subjects
Study design	Oral dose (200mg) at time 0, IV injection (0.4 mg for 15 minutes) at time 6h
Total n	11
Age, median (range), years	56 (45-65)
Weight, median (range), kg	76.6 (62.2-103.2)
% female (n %)	27.3

- A deconvolution algorithm [1] was used to derive individual input rate and percentage of bioavailable-dose.

- The population input rate was described with a Weibull distribution function [2] as follows:

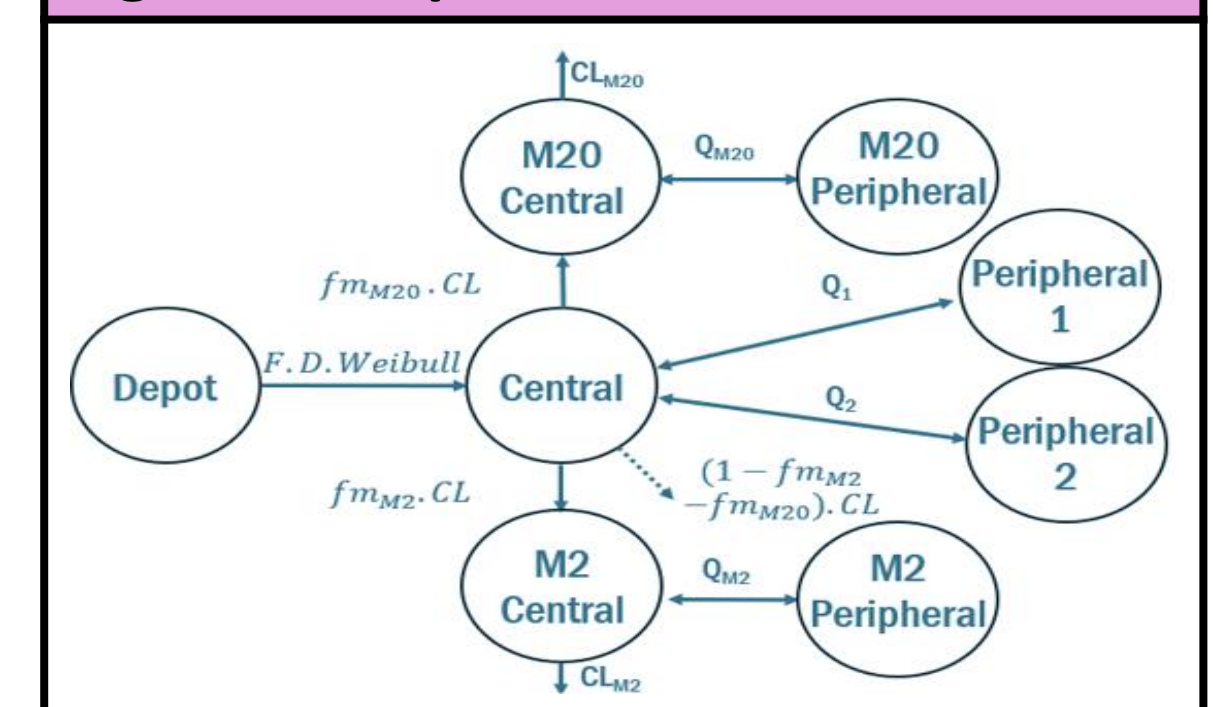
$$Weibull(t) = \lambda s(t - t_{lag})^{s-1} e^{-\lambda(t-t_{lag})^s}$$

where λ is an analogue of the absorption rate constant and s , a shape parameter.

- A finite absorption time [3] of 50 hours was included to restrict the Weibull function within an acceptable time span, based on the time required to cover 95% of the population absorption profile, as determined by the percentage of bioavailable dose results

- Monolix version 2023R1 was used for non-linear mixed effects modelling
- Different parent-metabolites models were tested with 1-, 2- or 3-compartment disposition models. The final model is displayed in **Figure 1**.
 - Hypothesis to ensure global identifiability, $V_{\text{central, parent}} = V_{\text{central, metabolite}}$
- Model performance was assessed by parameter estimates, goodness-of-fits and visual predictive checks (VPC).

Figure 1: PopPK model structure

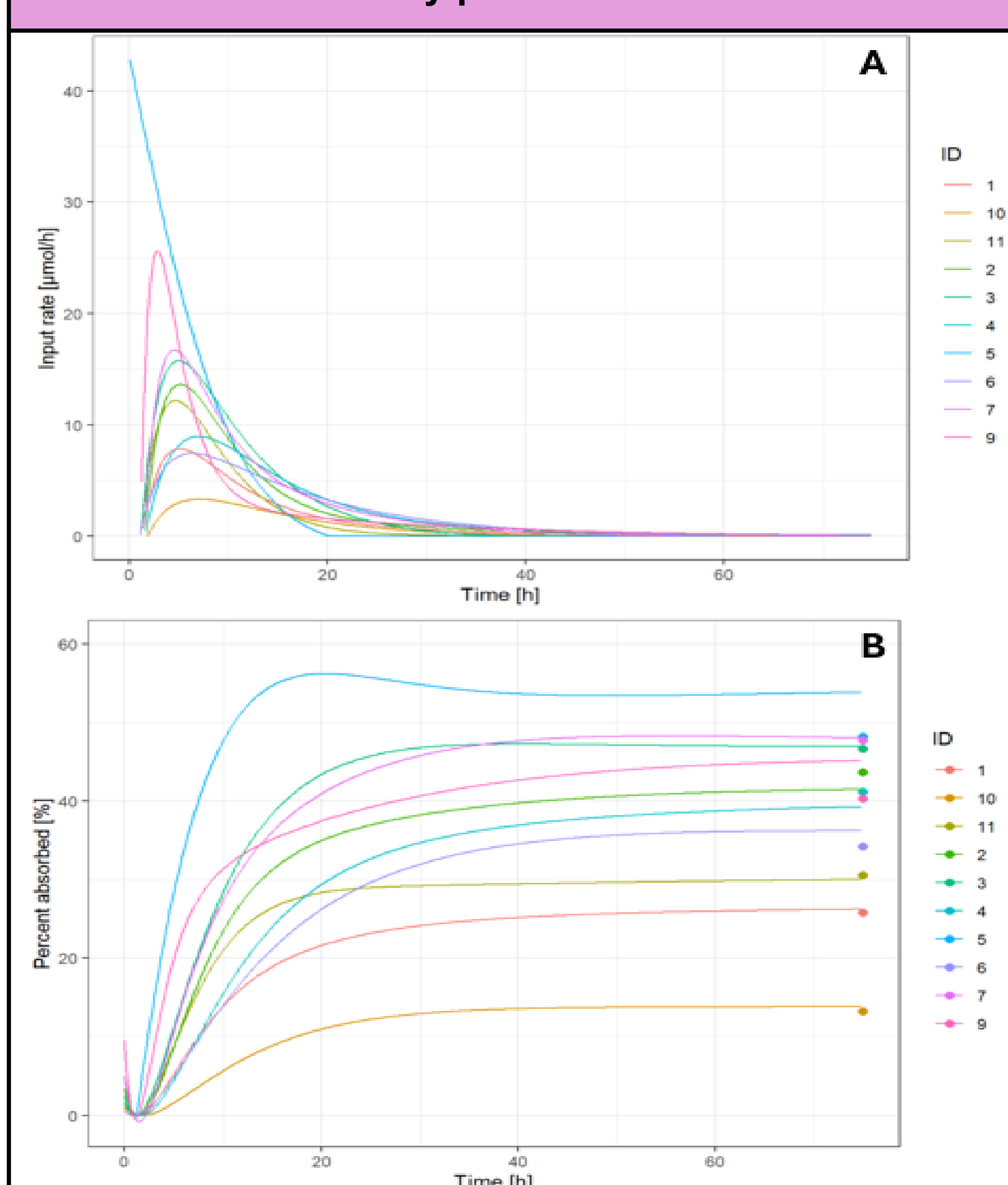


Results

Deconvolution approach

- The population deconvoluted input rate profiles (**Figure 2a**) showed:
 - a median lag time of 1.3h [range: 0-1.8]
 - a maximum input rate of 12.9 $\mu\text{mol/h}$ [range: 3.30-42.76]
 - a time to reach the maximum input rate of 5 h [range: 0-7] after the dose administration.
- The absorbed percentage of bioavailable-dose (**Figure 2b**) showed a median of 41 % [range: 12.8-53.75].

Figure 2: Deconvoluted population profiles of the absolute-bioavailability profile

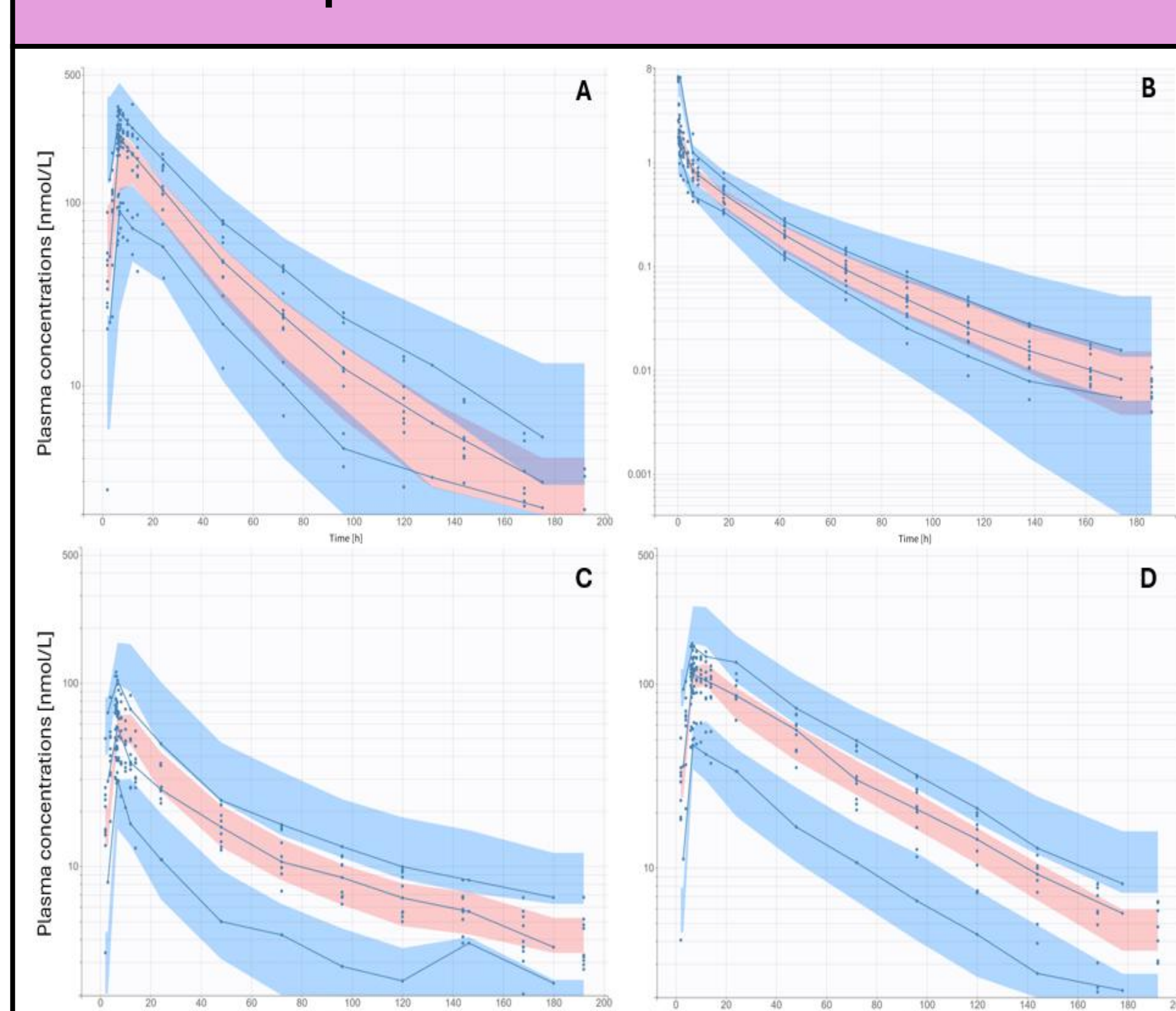


(a) The solid lines represent individual input rates. (b) The solid lines are the percentage of bioavailable-dose in the system for each individual. The solid dots depict the bioavailability obtained by the non-compartmental analysis as a comparison.

PopPK model

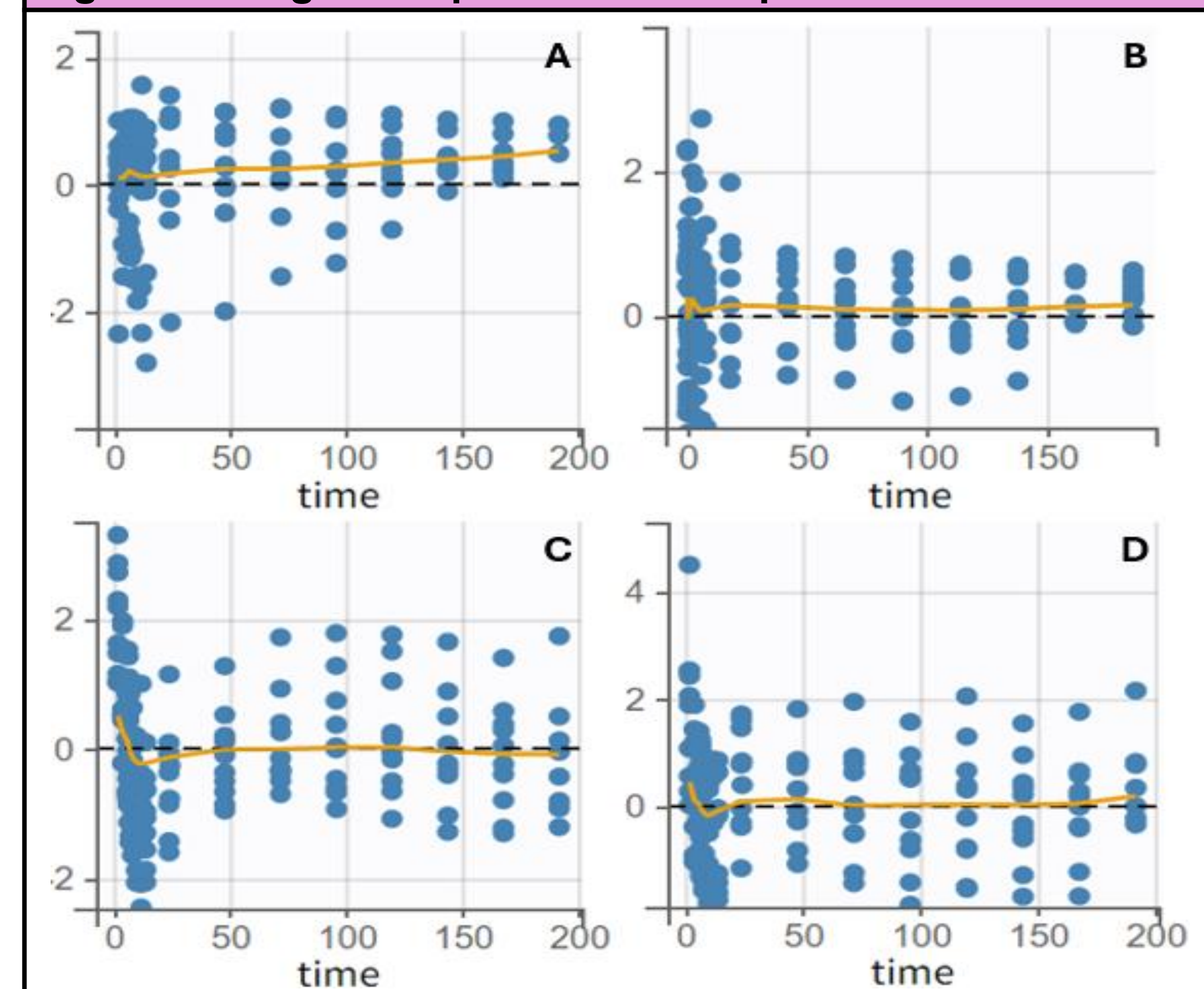
- Abemaciclib and its metabolite concentration datapoints that were below the limit of quantification ($< 1.97 \text{ nmol/L}$) represented $<10\%$ of the dataset and were not included in the modelling exercise.
- Overall, the model evaluation through the goodness-of-fit plots (**Figure 3 and 4**) and the PK parameter estimates (**Table 2**) showed a good description of the parent-metabolites data.

Figure 3: Visual predictive checks of the parent-metabolite PopPK



(A) Oral parent, (B) IV parent, (C) M2 metabolite and (D) M20 metabolite profiles. In each panel, the blue dots are the observed plasma concentrations. The solid blue lines represent the 5th, median and 95th percentiles of the observed concentrations. The red shaded area is the 90th confidence interval around the median. The blue shaded areas are the 90th confidence interval around the 5th and 95th simulated intervals.

Figure 4: Diagnostic plots for the PopPK model



(A) Oral parent, (B) IV parent, (C) M2 metabolite and (D) M20 metabolite profiles. The blue dots are the residuals displayed in each section with the population weighted residuals against (left) time or (right) population predictions. The dotted lines represent the line of identity and the yellow lines are the spline interpolation.

Table 2: Estimated parameter estimates

Parameters	Estimates	% R.S.E	BSV (CV%)	% R.S.E	Parameters	Estimates	% R.S.E	BSV (CV%)	% R.S.E
λ [h ⁻¹]	0.0065	26.5	100.56	22.6	fm_{M2} *	57.83	8.33	23.27	25.6
S	2.45	5.13	16.28	22.5	CL_{M2} [L/h] *	2497.89	5.83	10.68	48.7
F	0.39	10.1	29.72	22.4	Q_{M2} [L/h] *	2207.24	6.03	-	-
V_{central} [L]	56.85	29.1	114.56	22.5	$V_{M2, \text{peripheral}}$ [L] *	321452.04	13.8	-	-
$V_{\text{peripheral 1}}$ [L]	343.04	9.23	28.86	23.7	fm_{M20} *	77.76	5.67	13.99	28.9
$V_{\text{peripheral 2}}$ [L]	244.19	12.4	38.68	24.5	CL_{M20} [L/h] *	1974.29	7.16	19.35	25.5
Q1 [L/h]	125.23	5.83	17.31	25.5	Q_{M20} [L/h] *	1472.39	5.45	-	-
Q2 [L/h]	11.6	23.7	85.67	22.8	$V_{M20, \text{peripheral}}$ [L] *	37109.61	5.09	-	-
CL [L/h]	22.97	8.16	26.05	22.7	* Apparent parameters assuming $V_{\text{central, parent}} = V_{\text{central, metabolite}}$				
					Residual error	Distribution	Estimates	%R.S.E	
					Oral parent - additive	Lognormal	0.13	6.70	
					¹³ C-labelled IV - additive	Lognormal	0.19	6.45	
					M2 - additive	Lognormal	0.29	5.42	
					M20 - additive	Lognormal	0.17	5.47	

F: Bioavailability, $V_{\text{compartment}}$: compartment volume of distribution, Q: intercompartmental clearance, CL: clearance, fm: fraction metabolised

Contact

✉ frederic.lusoli@postgrad.manchester.ac.uk



www.capkr.manchester.ac.uk

Reference(s)

- [1] Veng-Pedersen P., *J Pharmacokinet Biopharm.* (1980) 8, 463-481.
- [2] Piotrovskii et al. *J Pharmacokinet Biopharm.* (1987) 15, 681-686.
- [3] Macheras, P., Tsekouras, A.A. *J Pharmacokinet Pharmacodyn* (2023) 50, 5-10.