

Development of a PopPK model for oral absorption of Abemaciclib

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

Context

- Abemaciclib is an orally administered anti-cancerous drug that produces two active metabolites, M2 and M20, contributing to over 10% of the abemaciclib-related exposure.
- The drug showed complex absorption, described by a number of complex absorption models in the literature, with mixed results [1,2].

Objectives

- Explore the abemaciclib absorption with a deconvolution method
- Develop a popPK model to describe parent-metabolite exposure after a single dose

Materials & Methods

- Development dataset:** Absolute bioavailability study (NCT02327143) in 10 subjects, based on a semi-simultaneous study of oral dose of Abemaciclib followed by intravenous administration of ¹³C-Abemaciclib, 6h later.
- Validation dataset:** Single-dose data of an induction study (NCT02256267) in 24 subjects and a food effect study (NCT02482935) in 30 subjects with fasted and fed states. A total of 4728 plasma concentrations were used for model development and validation.
- Deconvolution** - the input rate and percentage of the dose were derived using the algorithm developed by Veng-Pedersen [3] over time.
- Absorption** - a finite absorption time was defined as 50 hours, meaning that 95% of the dose was absorbed for each subject in the study (n = 10).
- Fraction metabolised (fm):** A PBPK model was developed in parallel to refine the fm parameters. The obtained parameter values and their variabilities were fixed in the popPK model.
- Modelling** - a Weibull function was used to describe the input rate in the popPK model (Figure 2) and combined with a three-compartment disposition model.

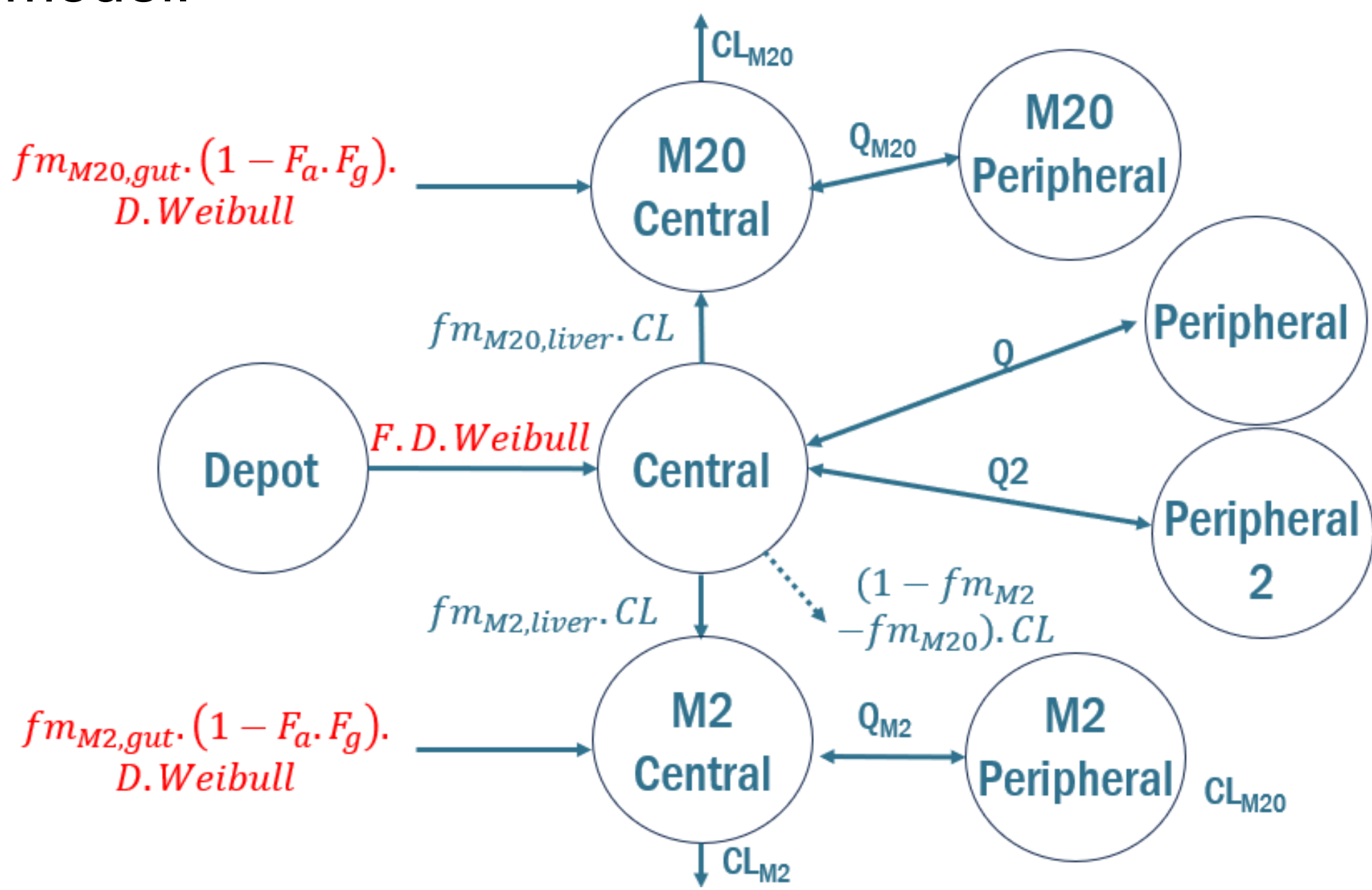


Figure 2. PopPK model structure

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 ⁻²]	0.0095	21.5	76.55	22.5	fm _{M2, gut}	0.18	-	57.35	-
S	2.25	4.54	14.4	22.5	V _{M2} [L]	19.12	3.96	10.34	31.2
F	0.39	10.9	31.83	22.4	V _{M2, peripheral} [L]	1046.47	2.28	-	-
V _{central} [L]	54.87	25.0	92.1	22.7	Q _{M2} [L/h]	78.17	1.94	3.28	63.1
V _{peripheral 1} [L]	420.83	11.0	35.19	23.0	CL _{M2} [L/h]	15.96	2.79	7.63	28.5
V _{peripheral 2} [L]	153.9	4.53	-	-	fm _{M20, liver}	0.000018	-	93.11	-
Q [L/h]	136.75	12.1	38.89	23.2	fm _{M20, gut}	0.069	-	64.43	-
Q2 [L/h]	4.99	3.36	8.52	30.6	V _{M20} [L]	4.96	3.52	10.4	25.3
CL [L/h]	22.33	10.9	26.42	22.7	V _{M20, peripheral} [L]	96.74	1.89	-	-
F _H	0.78	-	-	-	Q _{M20} [L/h]	23.86	2.15	3.63	70.9
fm _{M2, liver}	0.036	-	41.6	-	CL _{M20} [L/h]	2.04	4.10	12.35	24.2

Residual error	Distribution	Estimates	%R.S.E
Proportional error - Oral	Normal	0.14	6.15
Proportional error - ¹³ C-labelled IV	Normal	0.2	6.29
Additive error - M2	Lognormal	0.15	5.76
Additive error - M20	Lognormal	0.096	6.64

F: Bioavailability, V: Volume of distribution, Q: Intercompartmental clearance, CL: Clearance, F_H: fraction escaping the liver metabolism

Results

- The goodness-of-fit (GOF) using visual predictive check (VPC) showed adequate description of the data by the model, and parameters were well estimated. Overall, the model adequately described the absorption phase and the metabolite formation (Figure 3).

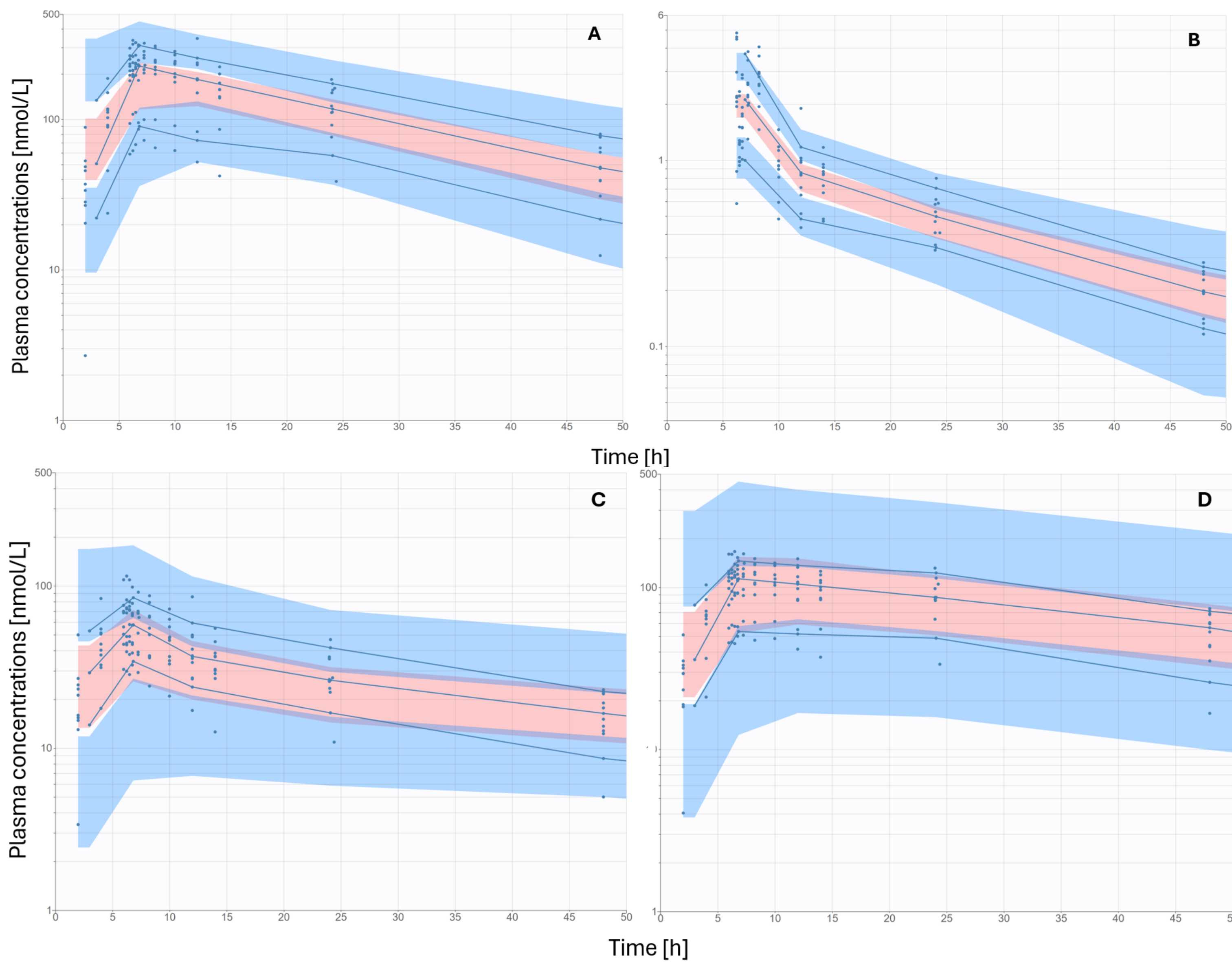


Figure 3. PopPK model VPCs of A) oral parent, B) I.V parent, C) M2 metabolite and D) M20 metabolite

Solid blue lines - 5th median, median and 95th percentiles of the observed concentrations
Red shaded area - 95% confidence interval around the median
Blue shaded areas - 95% confidence interval around 5th and 95th simulated intervals.

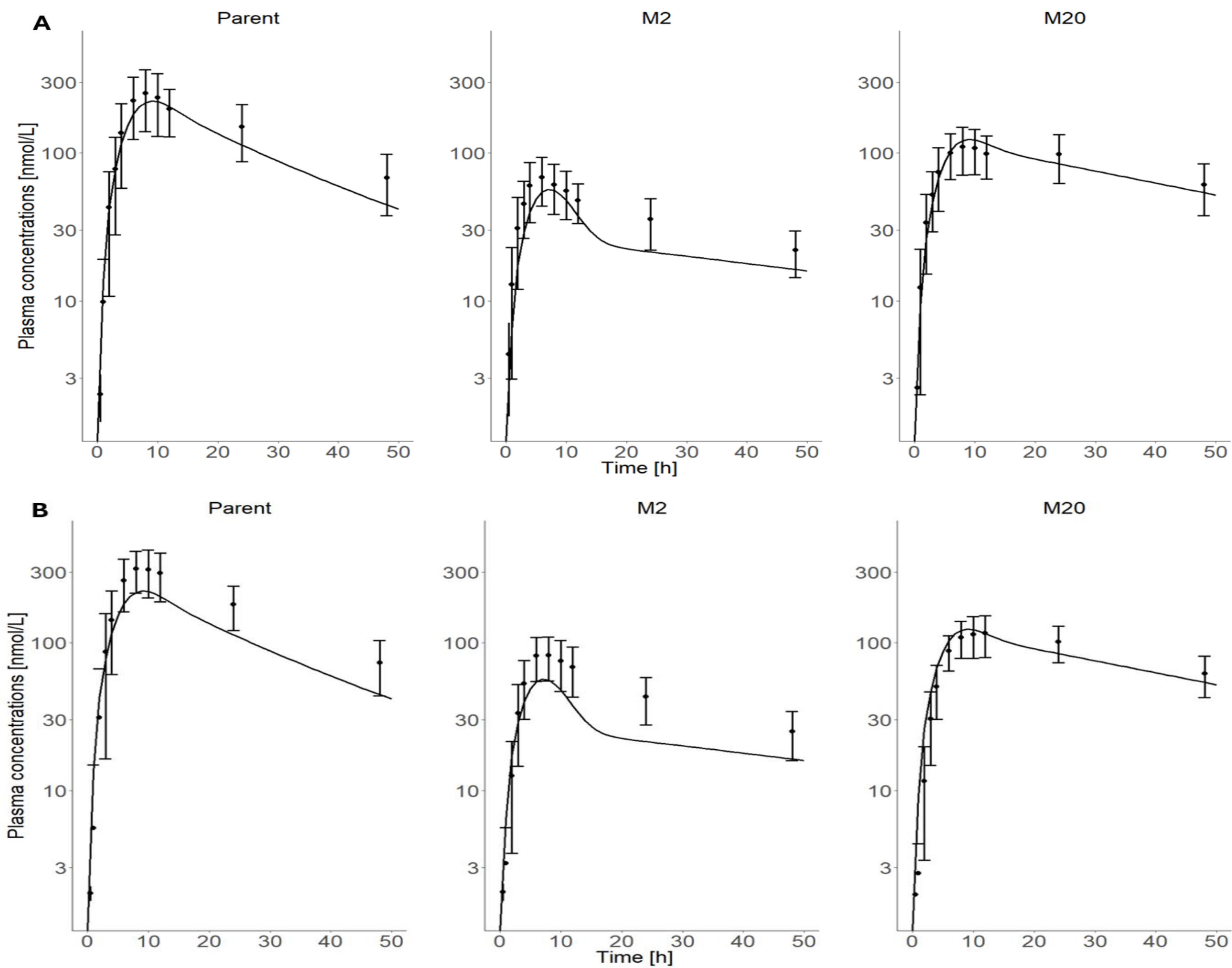


Figure 4. Model Validation: Parent-metabolite simulated (lines) and observed plasma concentrations data (dots: mean, error bars: standard deviation) for A) fasted and B) high-fat meal conditions.

Conclusion

The Weibull absorption model was used to describe the oral absorption of abemaciclib and its formation of metabolites across multiple clinical studies.

Reference(s)

- [1] Chigutsa et al. CPT:PSP (2020) 9, 523-533.
- [2] Posada et al. J Clin Pharmacol. (2020) 60, 915-930.
- [3] Veng-Pedersen P., J Pharmacokinet Biopharm. 1980;8(5):463-481.

