

Population PK model describing multiple secondary peaks after oral administration of buparlisib in healthy volunteers

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Background and Objective

- Buparlisib is an anticancer drug inhibiting the PI3K pathway [1] presently in Phase 3 development. Inspection of plasma PK profiles in healthy volunteers (HVs) and patients showed multiple secondary peaks after oral administration.
- Preclinical studies revealed an important role of biliary excretion and UGT enzyme to buparlisib elimination. Thus, entero-hepatic circulation (EHC) was considered as a reasonable hypothesis to explain multiple peaks phenomenon.
- Objective was to develop a PK model able to (i) describe the observed multiple peaks in healthy volunteers, (ii) confirm the physiological plausibility of EHC hypothesis and (iii) quantify EHC contribution to the buparlisib PK.

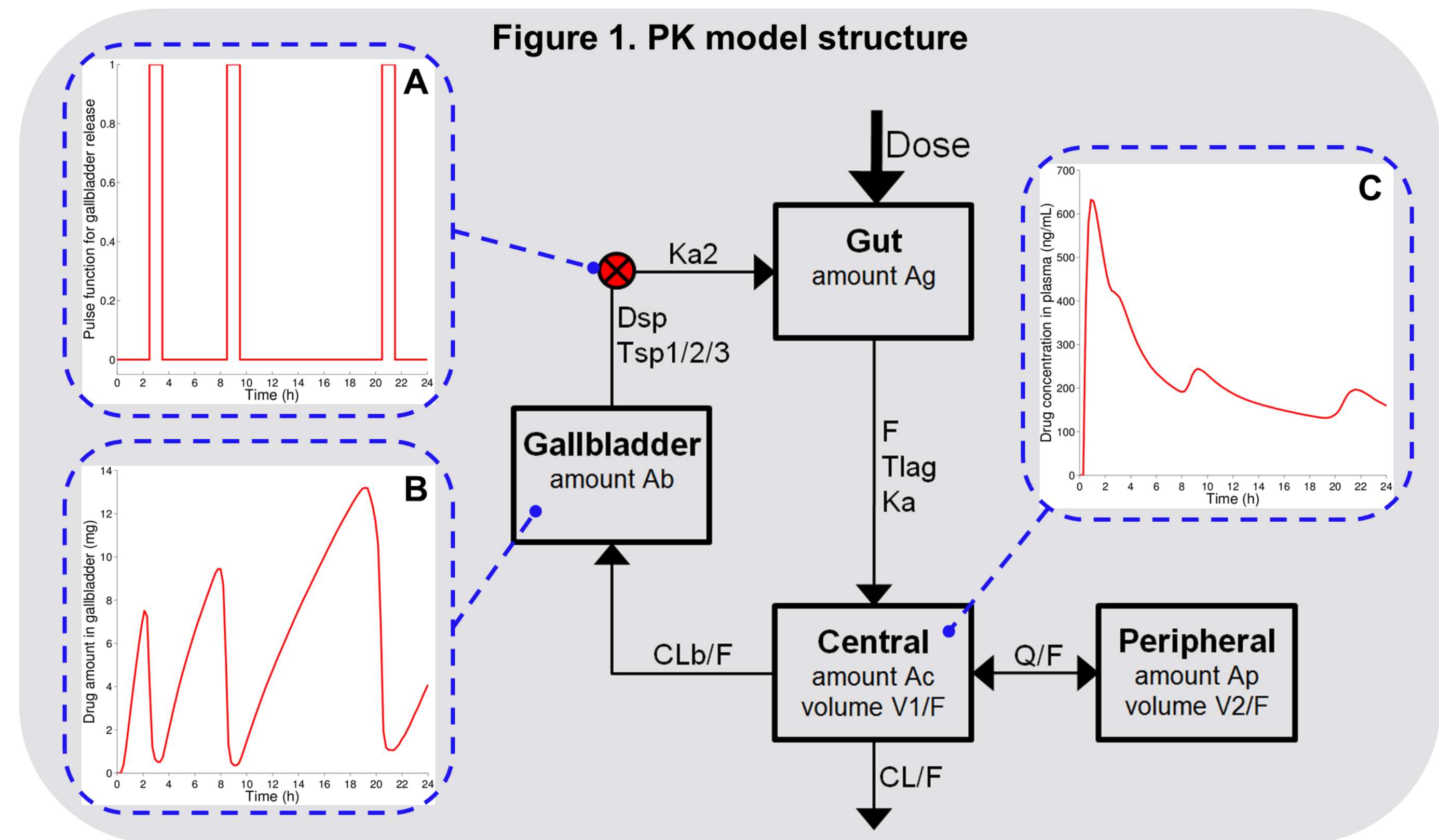
Conclusion

- Buparlisib multiple peaks occurring around meal times were well described by the proposed PK model confirming the physiological plausibility of EHC hypothesis. Fraction of dose excreted in bile and then reabsorbed was estimated at 10% suggesting EHC as an important component of buparlisib PK.
- These results were obtained by integration of preclinical knowledge and model based hypothesis leading to a new study design.
- The proposed PK model can be applied to multiple oral administrations and therefore will be used to analyze PK data in cancer patients.

PK model development

STEP 1: Develop and refine the PK model structure (3 studies)

- Plasma concentrations of 60 HVs from three Phase 1 studies collected after a single oral administration were used for the PK model development.
- A third compartment representing the gallbladder was added to a classical 2-compartment disposition model with first order absorption and elimination in order to mimic a potential biliary excretion of buparlisib (Figure 1).



- Drug amount in gut (Ag), central (Ac), peripheral (Ap) and gallbladder (Ab) compartments is described by a set of differential equations for $t > Tlag$:

$$\begin{aligned} dAg/dt &= Dose - F \cdot ka \cdot Ag + ka2 \cdot Ab \cdot aux \\ dAc/dt &= F \cdot ka \cdot Ag - (k12 + ke + kb) \cdot Ac + k21 \cdot Ap \\ dAp/dt &= k12 \cdot Ac - k21 \cdot Ap \\ dAb/dt &= kb \cdot Ac - ka2 \cdot Ab \cdot aux \end{aligned}$$
$$\begin{aligned} CL/F &= ke \cdot V1/F \\ CLb/F &= kb \cdot V1/F \\ Q/F &= k12 \cdot V1/F = k21 \cdot V2/F \end{aligned}$$

- Drug amount is continuously excreted in bile from central compartment and stored in gallbladder. Release of gallbladder content in gut at each meal time (Fig 1A-1B) is modeled with the pulse function $aux(t)$ combining 2 Heaviside step functions based on emptying time dsp , i^{th} meal time tsp_i and Heaviside slope h :

$$aux(t) = (f1(t) - f2(t))/dsp$$
$$f1(t) = 0.5 \cdot \left(1 + \sum_{i=1}^{i=3} \tanh(h \cdot (t - tsp_i)/tsp_i) \right)$$
$$f2(t) = 0.5 \cdot \left(1 + \sum_{i=1}^{i=3} \tanh(h \cdot (t - (tsp_i + dsp))/(tsp_i + dsp)) \right)$$

- Time of the i^{th} meal is computed relative to the dosing time as $t_i = t_{dose} + tsp_i$

STEP 2: Confirm drug recirculation hypothesis

- Based on modeling results an additional sampling time at 10h post dose around the second meal time was added to the design of a fourth Phase 1 study enrolling 16 HVs in order to obtain a better estimation of the second peak.

STEP 3: Final pooled analysis (4 studies)

- Plasma concentrations from the four Phase 1 studies were simultaneously analyzed and model parameters for absorption (Tlag, Ka), volumes (V1/F, V2/F), clearances (CL/F, CLb/F, Q/F) and meal times (Tsp1/2/3) were re-estimated.

ESTIMATION METHOD: population approach with Monolix 4.3.2 [2].

Results and Discussion

Main results

- Predicted concentrations were in agreement with observed values (Figure 3), multiple secondary peaks were well described (Figure 2) and all model parameters were accurately estimated (Table 1).
- Meal times estimated at 2.4, 8.3 and 20.3 h post dose were in agreement with respective theoretical times of lunch, dinner and breakfast at the next morning.
- Mean fraction of dose that goes into entero-hepatic circulation was estimated at 10% and computed as $Fb = kb/(kb + ke + k12)$.
- These results showed that for compounds having low clearance even a low contribution of biliary excretion might be impactful on the PK profile.

Model assumptions

- EHC is the cause of multiple secondary peaks and release of gallbladder content occurs only at 3 meal times per day.
- 90% of gallbladder content is released after each meal and 100% of the released amount is reabsorbed.

Model limitations

- Current model assumes constant lunch/dinner/breakfast times within a subject, further development should explore inter-occasion variability on meal times.

Figure 2 - Prediction distribution

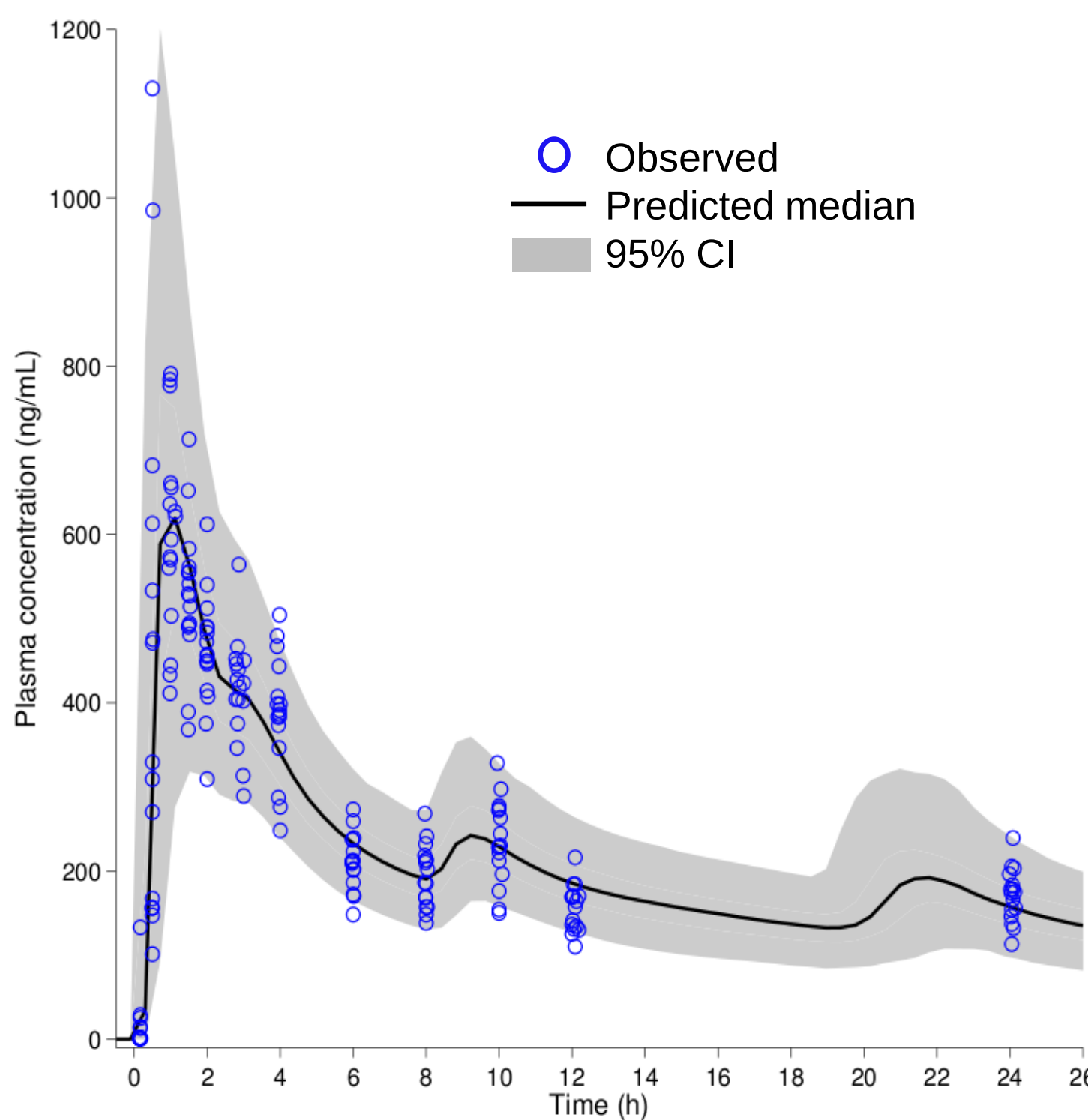


Figure 3 - Model evaluation

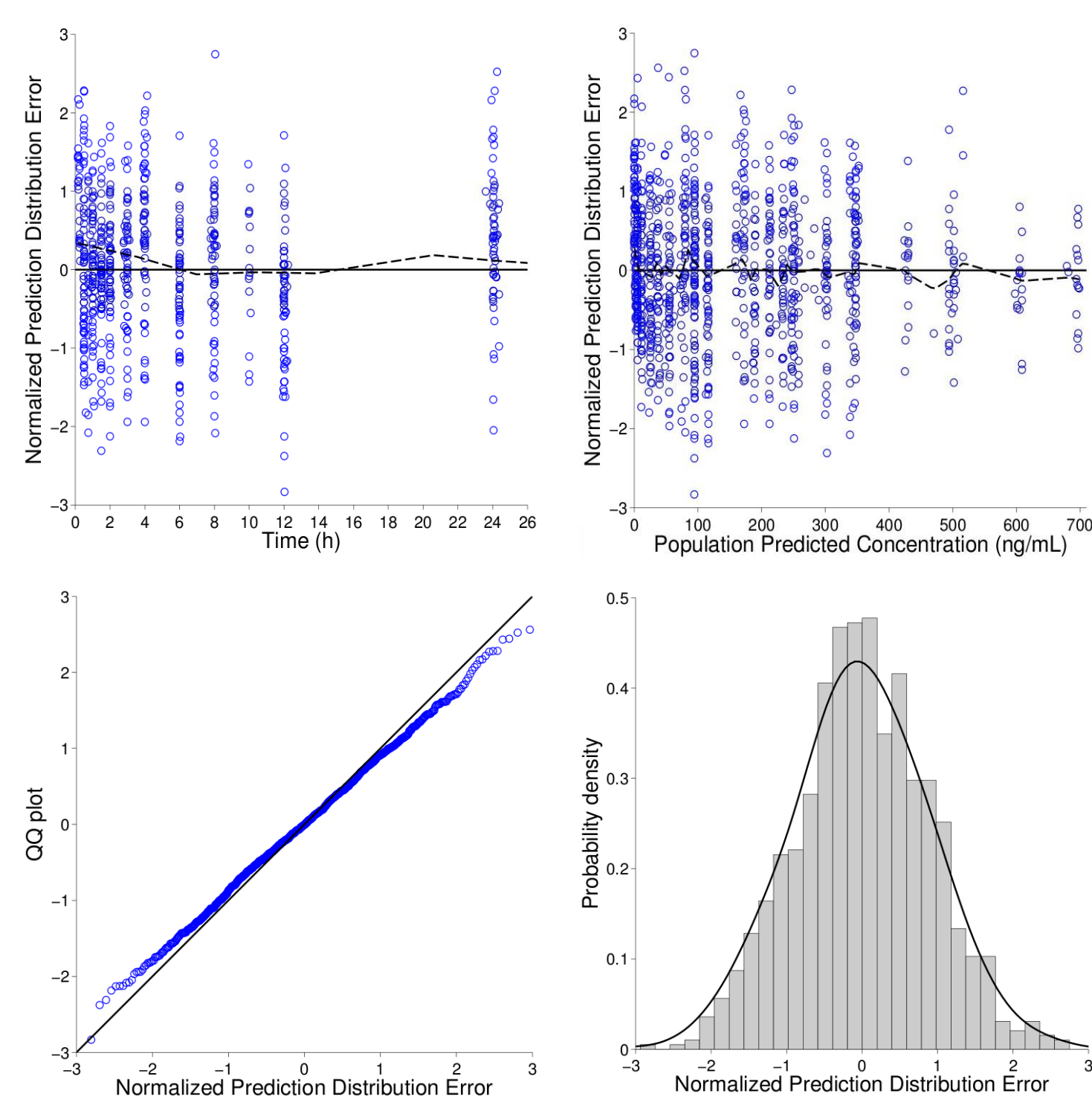


Table 1 - Model parameter estimates

PARAMETER		FIXED EFFECTS		INTER-SUBJECT VARIABILITY	
		Estimate	RSE%	Estimate	RSE%
Tlag	lag time (h)	0.29	4.95	0.41	8.82
F	relative oral bioavailability	1.00	FIX	0.00	FIX
Ka	absorption rate (h-1)	3.85	13.4	0.82	11.3
V1/F	central volume (L)	107	5.03	0.36	12.1
V2/F	peripheral volume (L)	231	3.88	0.27	10.6
Q/F	inter-compartmental clearance (L/h)	36.5	5.35	0.30	18.8
CL/F	clearance (L/h)	6.48	3.65	0.29	8.70
CLb/F	biliary clearance (L/h)	7.96	9.51	0.30	FIX*
Tsp1	time of Lunch (h)	2.43	3.47	0.10	FIX*
Tsp2	time of Dinner (h)	8.33	1.47	0.13	36.4
Tsp3	time of Breakfast (h)	20.3	1.18	0.20	FIX*
a	additive error (ng/mL)	0.73	7.57	0.00	FIX
b	proportional error (%)	0.17	2.70	0.00	FIX

Ka2: gallbladder release rate fixed to 8 h-1; Dsp: gallbladder emptying time fixed to 1h; h: Heaviside slope fixed to 30000; *: fixed to the reported value because not accurately estimated (RSE > 50%).

References:

- Cantley LC. Science 2002; 296(5573):1655-1657
- Kuhn et al. Computational Statistics and Data Analysis 2005; 49:1020-1038

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