The specific formulation of the semi-PBPK model is shown below.

It was assumed that no absorption and metabolism of drugs occurs in stomach. The amount (A_0) in stomach is controlled by the constant of gastric emptying rate ($K_{t,0}$), i,e

$$\frac{dA_0}{dt} = -K_{t0} \times A_0 \quad (S1)$$

Small intestine is divided into duodenum, jejunum and ileum, which is further divided into the gut lumen and the gut wall. Drug amount (A_i) in the i^{th} gut lumen is illustrated by

$$\frac{dA_i}{dt} = K_{t,i-1} \times A_{i-1} - K_{ti} \times A_i - k_{a,i} \times A_i \quad (S2)$$

Where $K_{t,i}$ represents the constant of intestinal transit rate. $k_{a,i}$ represents the absorption rate constant from the gut lumen to the gut wall, which may be calculated using equation,

$$k_{ai} = \frac{2 \times P_{eff,A-B}}{r_i} \quad (S3)$$

Where r_i is the intestinal radius. $P_{eff\ A\text{-}B}$ is effective permeability coefficient (P_{eff}) from gut lumen to gut wall. The P_{eff} ($\times 10^{-4}$) values were estimated using the in vitro apparent permeability coefficient of drugs ($P_{app} \times 10^{-6}$) in Caco-2 cells based the equation[1]:

$$LogP_{eff} = 0.4926 \times LogP_{app,Caco-2} - 0.1454 \quad (S4)$$

The drug concentration in the i^{th} gut wall (C_{GWi}) is expressed as follows:

$$\frac{V_{GWi} \times dC_{GWi}}{dt} = k_{a,i} \times A_i + Q_{GWi} \times C_{sys} - Q_{GWi} \times C_{GWi} \times R_b / K_{G:P} \quad (S5)$$

Where Q_{GWi} and $K_{G:P}$ represent the blood flow rate in i^{th} gut wall and ratio of drug concentration in intestinal wall to plasma, respectively. C_{GWi} and V_{GWi} represent separately drug concentration in the i^{th} intestinal and wall volume of the i^{th} gut wall. C_{sys} represent drug concentrations in the systemic compartment. R_b is the ratio of drug concentrations in blood to plasma.

The drug enters the liver through the portal vein and the concentration in the portal vein (C_{PV}) is:

$$\frac{V_{PV} \times dC_{PV}}{dt} = \sum Q_{GWi} \times C_{GWi} \times R_b / K_{G:P} - Q_{PV} \times C_{PV} \quad (S6)$$

Q_{PV} and C_{PV} represent portal vein blood flow rate and volume of portal vein, respectively.

It was assumed that metabolism of CES1-mediated drugs mainly occurs in liver. Drug concentration (C_L) in liver is illustrated by

$$\frac{V_L \times dC_L}{dt} = Q_{PV} \times C_{PV} + Q_{LA} \times C_{sys} - Q_L \times C_L \times R_b / K_{L:P} - CL_{int} \times f_{u,b} \times C_L \times R_b / K_{L:P} \quad (S7)$$

Where Q_{LA} and Q_L represent the hepatic artery blood flow rate to the liver and hepatic blood flow to the systemic compartment, respectively. V_L and $K_{L:P}$ represent the volume of liver and ratio of drug concentration in liver to plasma, respectively. CL_{int} and $f_{u,b}$ represent intrinsic clearance in the liver and free fraction of drug in blood, respectively. $f_{u,b}$ is generated from the fraction unbound in plasma ($f_{u,p}$), i.e

$$f_{u,b} = \frac{f_{u,p}}{R_b} \quad (S8)$$

CL_{int} can be estimated using in vitro enzyme kinetics from human hepatic microsomes.

$$CL_{int} = \sum \frac{V_{max,i}}{K_{m,i} + f_{u,b} \times \frac{A_L \times R_b}{V_L \times K_{L;P}}} \approx \sum \frac{V_{max,i}}{K_{m,i}} \quad (S9)$$

Where $V_{max,i}$ and $K_{m,i}$ represent the maximum velocity and Michaelis-Menten constant in vitro enzyme kinetic experiments, respectively.

Hepatic clearance (CL_L) of a drug may be derived from total CL (CL_T) and renal CL (CL_K), i.e

$$CL_L = CL_T - CL_K \quad (S10)$$

Thus, The CL_{int} is also recalculated by hepatic blood clearance ($CL_{L,b}$) using equation

$$CL_{L,b} = \frac{Q_L \times f_{u,b} \times CL_{int}}{Q_L + f_{u,b} \times CL_{int}} \quad (S11)$$

The CL values by clinic are often plasma clearance of drug (CL_P), which may be transferred to blood clearance (CL_b) using equation 12.

$$CL_b = \frac{CL_p}{1 - Hct + R_b \times Hct} \quad (S12)$$

Where Hct is hematocrit, 0.43 in healthy subjects[2].

Some metabolites of some drugs are also eliminated via bile. Amount of metabolites ($A_{L,m}$) in liver is illustrated by equation 13.

$$\frac{V_L \times dC_{L,m}}{dt} = Q_{PV} \times C_{PV,m} + Q_{LA} \times C_{sys,m} + CL_{int,CSE1} \times f_{u,b} \times C_L \times R_b / K_{L:p} - Q_L \times C_{L,m} \times R_{b,m} / K_{L:P,m} - (CL_{int,m} + CL_{int,b,m}) \times f_{u,b,m} \times C_{L,m} \times R_{b,m} / K_{L:P,m} \quad (S13)$$

Where $CL_{int,b,m}$ and $CL_{int,m}$ are intrinsic bile clearance and intrinsic metabolic clearance, respectively. If metabolism of the metabolite did not occur in the body, the $CL_{int,b,m}$ may be recalculated from CL_K using equations 10 and 11.

Kidney is involved in elimination of drugs, especially their metabolites. Amount of drugs in kidney is illustrated by equation

$$\frac{V_K \times dC_K}{dt} = Q_K \times C_{sys} - (Q_K + f_{u,b} \times CL_{int,K}) \times C_K \times R_b / K_{K,P} \quad (S14)$$

Where Q_K and V_K represent kidney blood flow and volume of the kidney, respectively. $CL_{int,K}$ and $K_{K,P}$ represent intrinsic clearance in kidney and tissue-to-plasma concentration ratio in the kidney, respectively. $CL_{int,K}$ was also estimated from CL_K using equation 11.

Disposition of drugs in the systemic compartment is illustrated using one-compartment, two-compartment model or three-compartment model.

For one-compartment model

Drug concentration (C_{sys}) in systemic compartment

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:p} + Q_K \times C_K \times R_b / K_{K:p} - (Q_{LA} + Q_K) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (S15)$$

For two-compartment model

Drug concentration (C_{sys}) in systemic compartment.

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:P} + Q_K \times C_K \times R_b / K_{K:P} + k_{21} \times A_p - k_{12} \times V_{sys} \times C_{sys} - (Q_K + Q_{LA}) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (S16)$$

$$\frac{dA_P}{dt} = k_{12} \times V_{sys} \times C_{sys} - k_{21} \times A_P \quad (S17)$$

For three-compartment model

Drug concentration (C_{sys}) in systemic compartment.

$$\frac{V_{sys} \times dC_{sys}}{dt} = Q_L \times C_L \times R_b / K_{L:P} + Q_K \times C_K \times R_b / K_{K:P} + k_{21} \times A_{p1} - k_{12} \times V_{sys} \times C_{sys} + k_{31} \times A_{p2} - k_{13} \times V_{sys} \times C_{sys} - (Q_K + Q_{LA}) \times C_{sys} - \sum Q_{GWi} \times C_{sys} \quad (S18)$$

$$\frac{dA_{P1}}{dt} = k_{12} \times V_{sys} \times C_{sys} - k_{21} \times A_{P1} \quad (S19)$$

$$\frac{dA_{P2}}{dt} = k_{13} \times V_{sys} \times C_{sys} - k_{31} \times A_{P2} \quad (S20)$$

Where V_{sys} represents the apparent distribution volume in systemic compartment. A_P and A_{P1} are the amount of drug in two peripheral compartments. k_{12}, k_{21}, k_{13} and k_{31} represent the transfer rates between the systemic compartment and peripheral compartment.

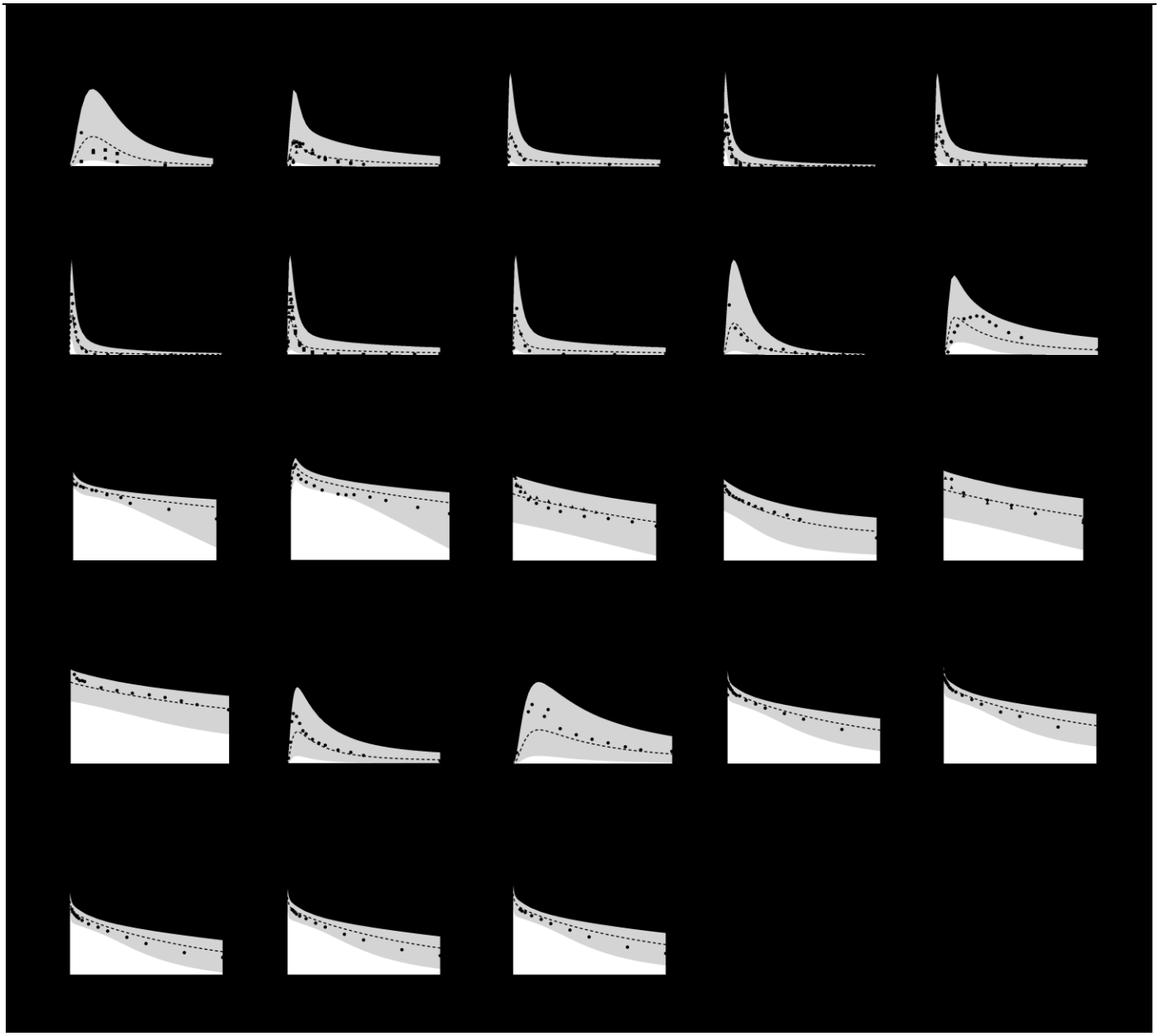

Figure S1. The observed (points) and predicted (lines) plasma concentrations of the tested CES1 substrates and their active metabolites following intravenous or oral administration to healthy subjects. Benazepril **(A)**[3,4] and benazeprilat **(B)**[3-5] following oral 10 mg benazepril hydrochloride; cilazapril **(D**, **F)**[6,7] and cilazaprilat **(C**, **E**, **G**, **H)**[6-9] following oral 1.25, 2.5, 5, 10 mg cilazapril; oseltamivir **(I)**[10] and oseltamivir carboxylate **(J)**[10] following oral 150 mg oseltamivir phosphate; flumazenil following intravenous 10 mg/1 min **(K)**[11] and 10mg/10min **(L)**[12]; pethidine following intravenous 50 mg/1min **(M)**[13], 25mg/1min **(N)**[14], 0.8mg/kg,1min **(O)**[15] and 0.8mg/kg,5min **(P)**[16]; pethidine hydrochloride and oral 25 mg **(Q)**[14], 0.8mg/kg **(R)**[16] pethidine hydrochloride; remimazolam following intravenous 0.05 **(S)**[17], 0.075 **(T)**[17], 0.2 **(U)**[17], 0.3 **(V)**[17], 0.4 **(W)**[17] mg/kg remimazolam besylate. Shaded areas indicate the 5th and 95th percentiles of simulations derived from 1000 virtual individuals. The dashed lines indicate the mean of the simulated profiles.

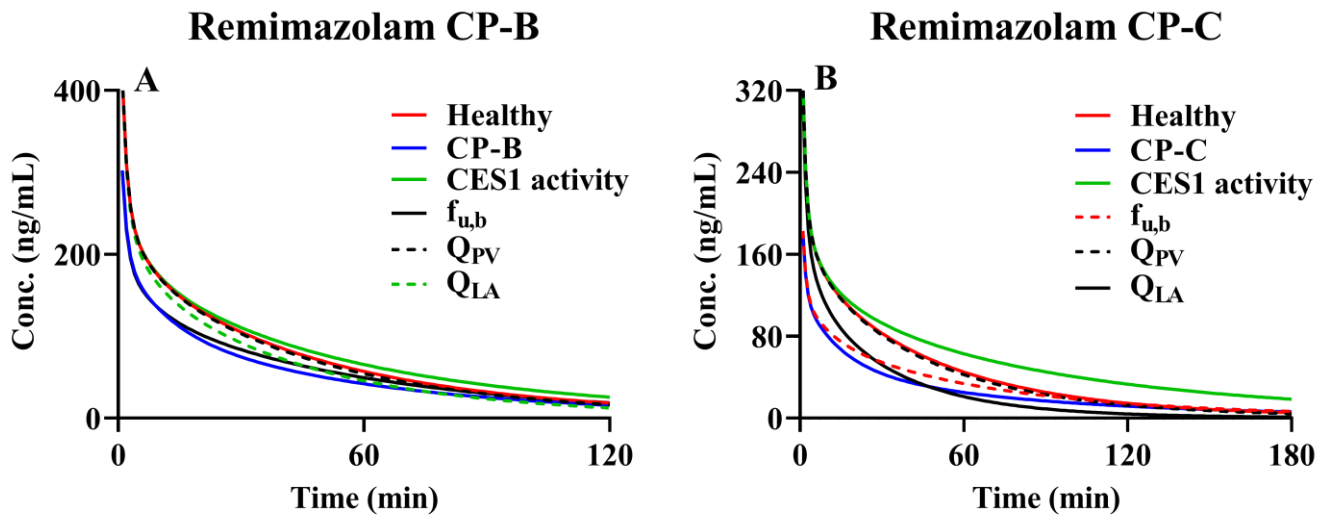

Figure S2. Contributions of LC-induced alterations in $f_{u,b}$, CES1 activity, Q_{LA} and Q_{PV} to plasma concentration of remimazolam following 10.4mg (CP−B, A) and 8.2mg (CP−C, B) administration to healthy human and LC patients.

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