Supplementary Information

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Guiding Dose Adjustment of Amlodipine after Co-administration with Ritonavir Containing Regimens Using a Physiologically-Based Pharmacokinetic/Pharmacodynamic Model

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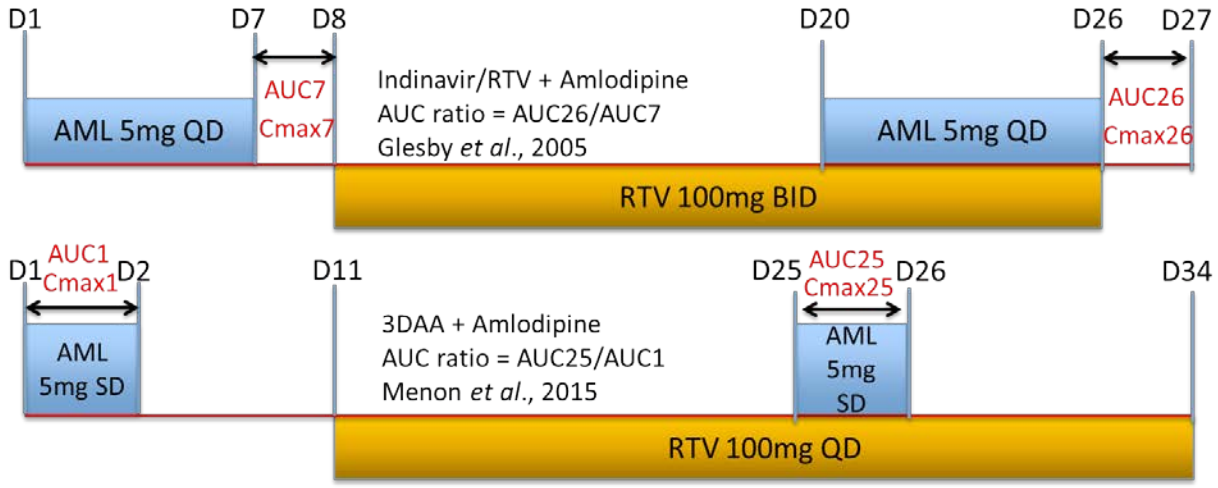

Figure S1: Clinical study designs of published clinical drug-drug interaction (DDI) studies of amlodipine with ritonavir (RTV)-containing regimens (3DAA refers to the combination regimen of ombitasvir/paritaprevir/RTV + dasabuvir).

AML, amlodipine; AUC, area under the plasma concentration-time curve; BID, twice daily; C_{max}, maximum plasma concentration; D, day; QD, once daily; SD, single dose; AUC1: AUC on day 1 and similarly for others; Cmax1:Cmax on day 1 and similarly for others

```
function indirectAlgebraicStep(t, xin, ...)
   -- Effect of amlodipine on systolic blood pressure
   local Po = 148.84 -- Baseline SBP (mmHg)
   local A = 8.245 -- Pressure amplitude (mmHg)
   local om = 0.463 -- cyclic frequency (1/hr)
   local m = -1285.93 -- Pressure slope (mmHg/mu-M)
   local keo = 0.049 -- Decay from effect compartment (1/hr)
   local t1 = 24 * math.floor(t/24) -- Time scaling to get clock time
   xout = Po + A * math.cos(om * (t - t1)) + m * xin * (1 - math.exp(-keo * t))
   return xout
end
```

Figure S2: *Lua* script used to define the pharmacodynamic (PD) model for systolic blood pressure within Simcyp V15R1; Parameter definitions are described in the code in green. The equation for *xout* follows the PD model equation as described in Equation 3 in the main text.

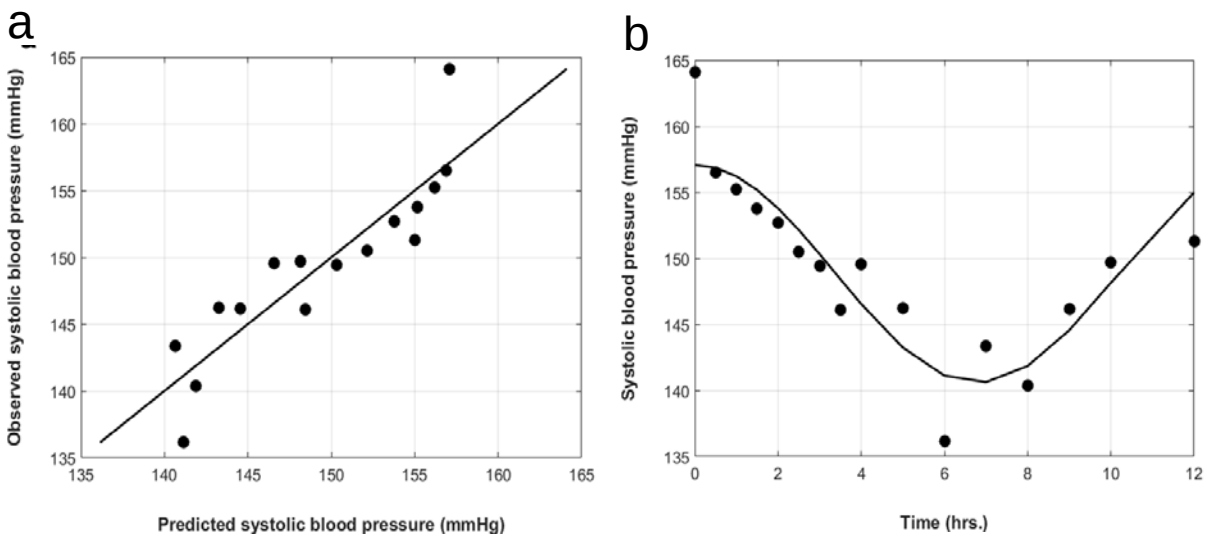

Figure S3: Diagnostic plots for the placebo model fit: (a) Goodness of fit plot of observed versus predicted systolic blood pressure (black solid line represents the line of unity); (b) visual predictive check plot for the placebo model (black solid line represents model prediction while black dots represent observed data); Observed data from Donnelly *et al.*, 1993

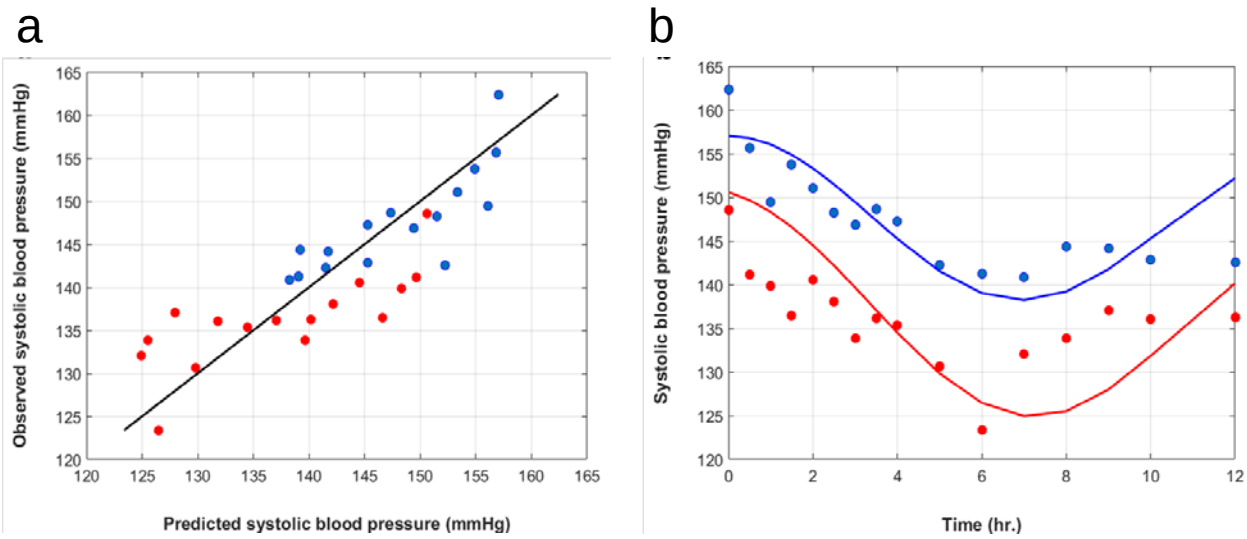

Figure S4: Diagnostic plots for the complete pharmacodynamic (PD) model fit: (a) Goodness of fit plot of observed versus predicted systolic blood pressure (black solid line represents the line of unity while red and blue dots represent points for day 1 and day 43 respectively); (b) visual predictive check plot for the complete PD model (red and blue colors reresent day 1 and day 43, respectively, while solid lines represent model prediction and dots represent observed data); Observed data from Donnelly *et al.*, 1993

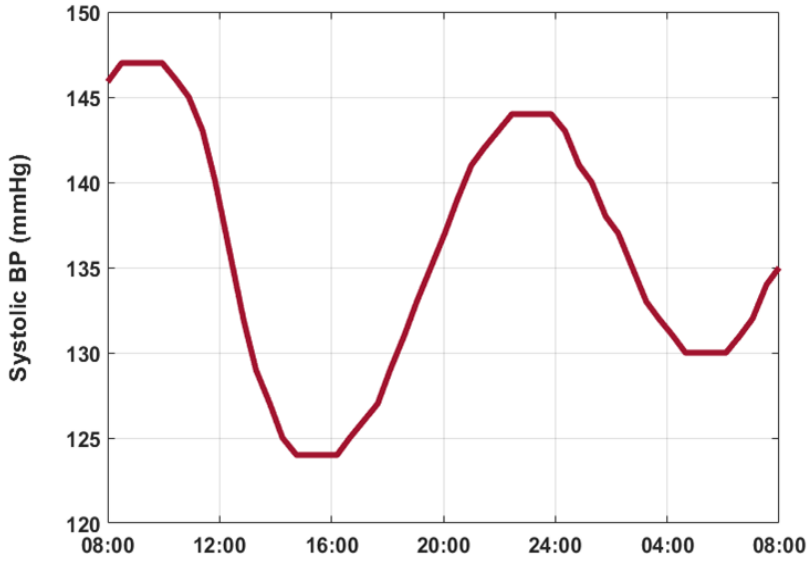

Figure S5: Model predicted systolic blood pressure over a 24-hour span for a virtual subject on amlodipine 5 mg daily dose at steady-state (after 6 weeks)

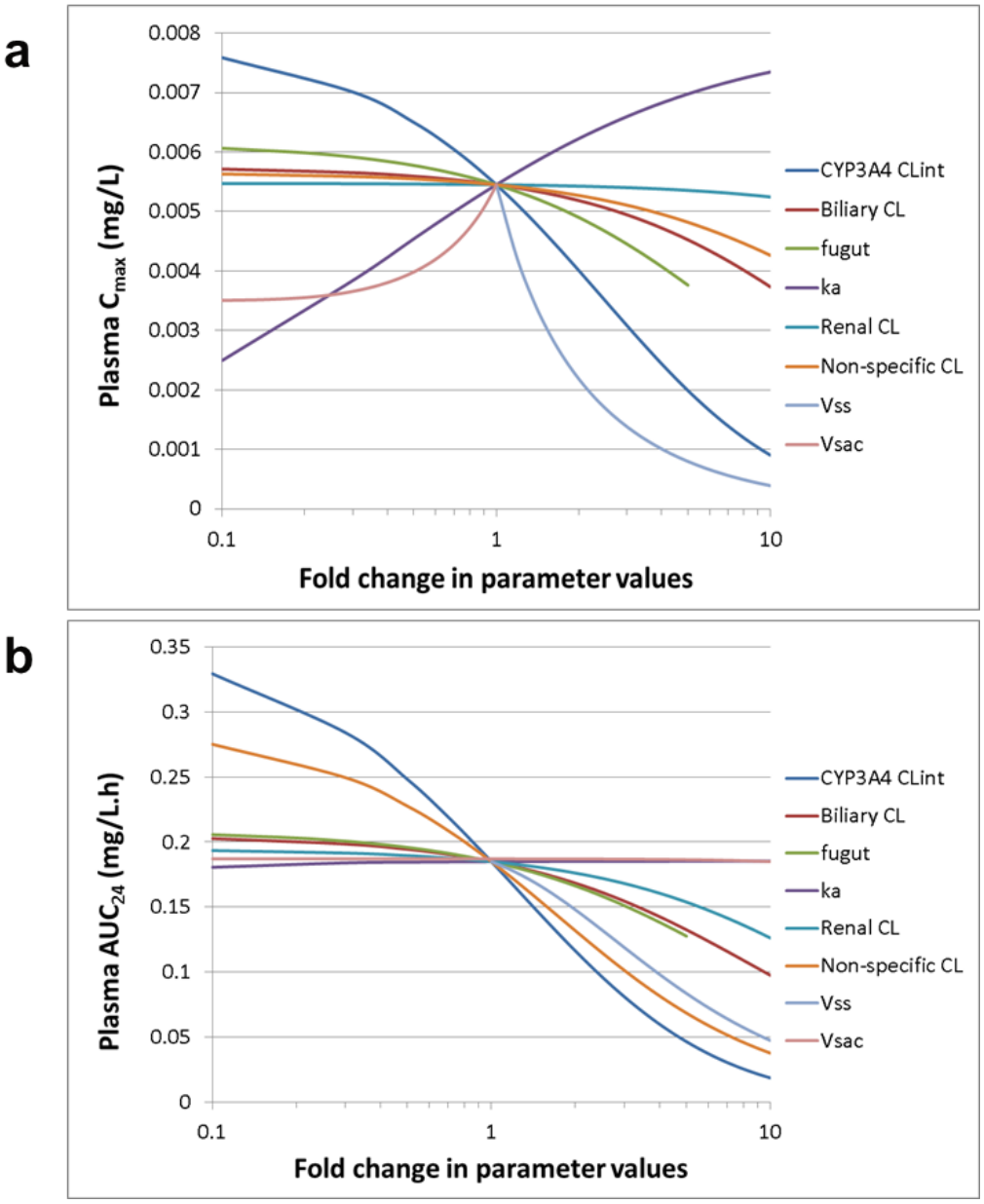

Figure S6: Results of local sensitivity analysis for 8 parameters in the PBPK model with (a) C_{max} and (b) 24-hour AUC as output variables; Parameter values were changed from their final values in the model by 10 fold in either direction (nominal value represented by 1). y-axis represents (a) maximum plasma concentration (C_{max}) and (b) area under the plasma concentration curve integrated over 24 hours.

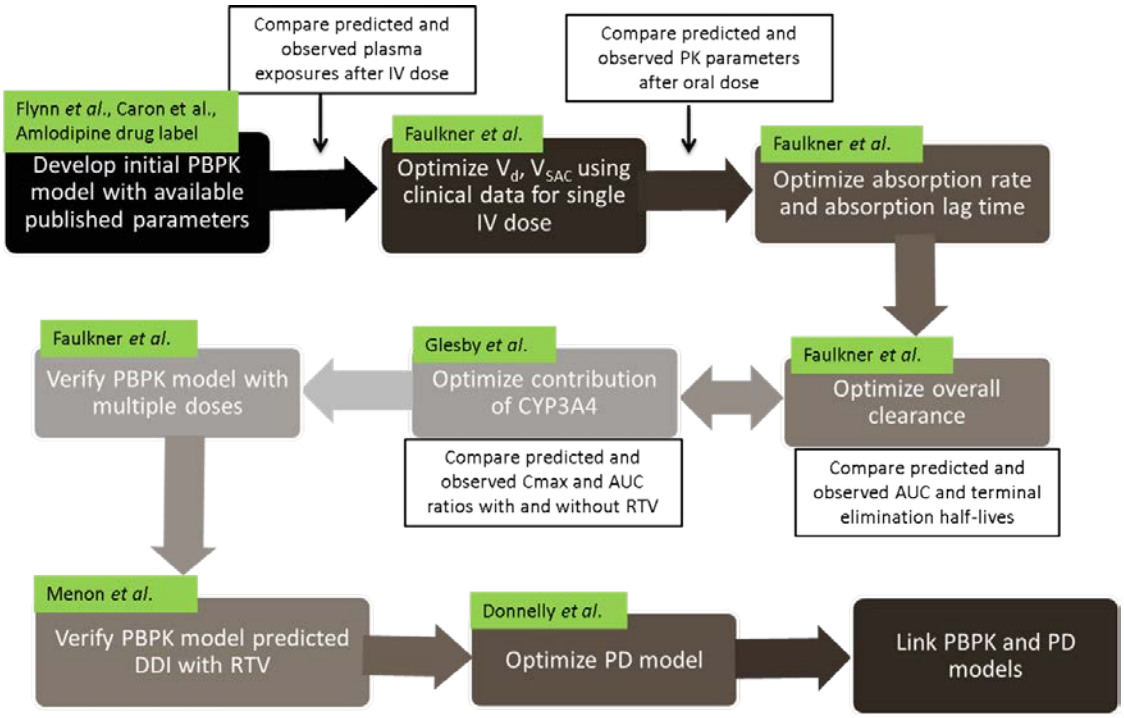

Figure S7: Flow diagram describing the model development and decision processes along with the data sources used in each step.

Assumption	Justification	Implication
1st order absorption model	• Model parsimony • BCS class I compound with high rate of absorption • Main motive of model is to predict DDI and not changes in pharmaceutics characteristics	Changes in the oral absorption model does not affect the overall DDI results with RTV
Fraction absorbed = 1	Human mass balance study found same amlodipine recovery in feces after oral and IV administration (Stopher *et al.*, 1988)	Change in fraction absorbed would affect the initial part of the plasma concentrations
Minimal PBPK model for distribution	Amlodipine distribution into other tissues is not an important consideration and plasma exposure is sufficient for prediction of efficacy; no known tissue uptake transporters involved	Amlodipine concentration in tissues other than the liver, gut, and blood cannot be predicted by the model
Biliary clearance	Amlodipine shown to undergo entero-hepatic recirculation (Rausl *et al*., 2006; Stopher *et al.*, 1988)	No significant effect
Minor renal elimination	Renal elimination only 6% (Beresford *et al*., 1988) Renally impaired patients had no change in plasma exposure compared with healthy subjects (Laher *et al*., 1988)	No significant effect
Additional non-specific systemic clearance	No other enzymes or transporters have been indicated to be contributing to amlodipine clearance	This ensures agreement of the overall predicted clearance with observed clearance while maintaining known pathway contributions such as CYP3A4 compared with the observed data
Systolic blood pressure is the appropriate pharmacodynamic variable	SBP has been indicated to be an important predictor of cardiovascular disease. (Canale *et al*., 1991). It is also more important to control SBP than diastolic blood pressure. (Byyny *et al*., 1997)	This ensures that clinical dose adjustments are related to the key clinical endpoint and outcome

Table S1: List of assumptions made during PBPK/PD model development

Study	Population	Age (year)	n	Amlodipine Dose
Faulkner et al., 1986	Healthy	25.8 ± 3.8	12	10 mg
Williams & Cubeddu, 1988	Healthy	23 - 34	12	10 mg
Sasaki et al., 2001	Hypertensive	78 ± 9	8	5 mg
Rausl et al., 2006	Healthy	-	24	10 mg
Lv et al., 2014	Healthy (Chinese)	-	12	10 mg
Elliott et al., 1988	Healthy	72 ± 6.3	16	5 mg
Faulkner et al., 1989	Healthy	24.3 ± 3.4	12	20 mg
Stopher et al., 1988	Healthy	-	2	15 mg
Donnelly et al., 1993	Hypertensive	25 – 64	12	5 mg

Table S2: Summary of subject demographics for clinical studies with amlodipine

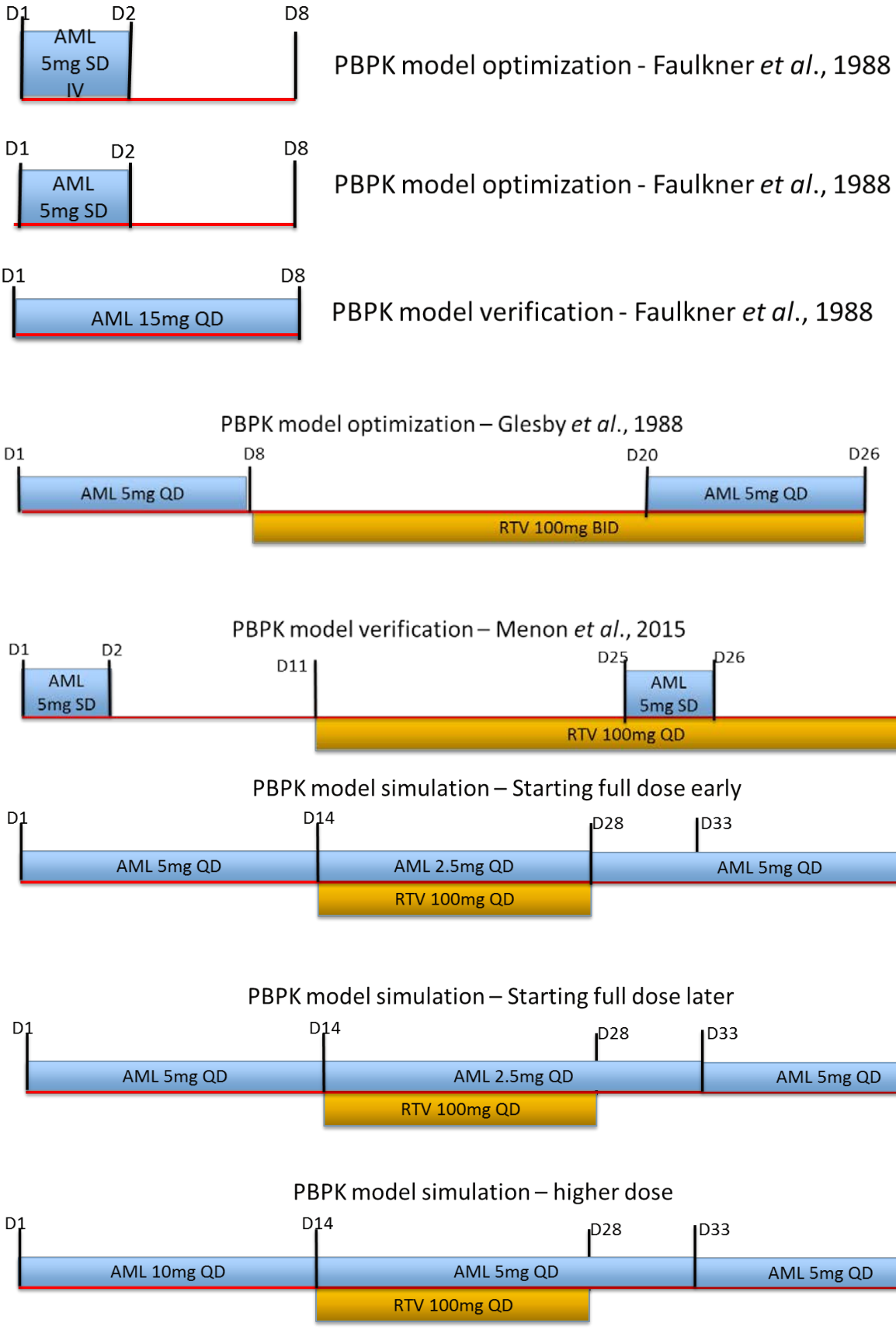

Figure S8: Simulation trial designs conducted using the final PBPK model in Simcyp