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Leveraging Physiologically Based Modelling to Provide Insights on the Absorption of Paliperidone Extended Release Formulation under Fed and Fasting Conditions

Supplementary Materials

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Table S1. Input parameters used to build the PBAM model in GastroPlus version 9.8

Parameter	Value	Source
Solubility at pH 6.8	0.39 mg/mL	[1]
Pka	2.6, 8.2	[2]
SolFactor	302.4(Pka=2.6), 4.429 (Pka=8.2)	Fitted to literature reported solubility [1] vs pH curve
Log P	1.02	[3]
Mean precipitation time	900 sec	GastroPlus version 9.8
Diff. coefficient	0.63 cm^2/sec X 10^5	ADMET predictor 9.5
Drug particle density	1.2 g/ml	ADMET predictor 9.5
Caco-2 permeability (Basolateral to Apical)	30.9 cm/s X 10^{-5}	[4]
Caco-2 permeability (Apical to Basolateral)	1.62 cm/s X 10^{-5}	[4]
Caco-2 permeability (Geometric Mean)	2.24 cm/s X 10^{-5}	[4]

S1. Input parameters used to build the PBAM model in GastroPlus version 9.8 (Continuation)

Structure	.sdf file of 2D structure	[3]
Molecular weight	426.49 g/mol	ADMET predictor 9.5
Molecular Formula	C23H27FN4O3	ADMET predictor 9.5
C1 for fasted or fed model	0.06944	Default GastroPlus version 9.8 (Human Physiology Fasted/Fed)
C2 for fasted or fed model	0.43028	Default GastroPlus version 9.8 (Human Physiology Fasted/Fed)
C3 for fasted or fed model	0.6	Fitted from 0.12147
C4 for fasted or fed model	0.8	Fitted from 0.46632
Volume of fluid in small intestine (ACAT model)	7.5%	Adjusted from 40% [5]
Volume of fluid in colon (ACAT model)	2%	Adjusted from 10% [5]
Renal Clearance (L/h/Kg)	0.0428	[6]
FPE (%)	2.78	[6]
K12	0.36846	Estimated by 3- compartment fit
K21	0.5136	Estimated by 3- compartment fit
K13	0.01457	Estimated by 3- compartment fit
K31	0.02098	Estimated by 3- compartment fit

Table S2. Comparison of simulated versus observed average PK parameters and metrics of single simulation of the oral solution under fasted condition

Parameter	Simulated Values	Observed Values	%PE
Fa (%)	99.888	N.A	N.A
FDp (%)	99.886	N.A	N.A
F (%)	97.102	N.A	N.A
C_{max} (ng/mL)	8.9655	8.5153	5.29%
T_{max} (h)	1.32	1.6102	-18.02%
$AUC_{0\text{-}inf}$ (ng-h/mL)	182.34	182.65	-0.17%
$AUC_{0\text{-}t}$ (ng-h/mL)	178.21	182.65	-2.43%

Fa(%), FDp (%), F(%) represent fraction absorbed across the apical membrane of the enterocyte, fraction absorbed reaching the portal vein, fraction bioavailable respectively, expressed as percentage of dose ; N.A: Not available.

Table S3. Verification of the PBAM model for the 2 mg PAL oral solution with external data from the literature

PK metrics (units)	Reported values*	Simulated values	Prediction Error (%)
	Mean (%CV)	Mean (%CV)	
Cmax (ng/ml)	19.4 (34%)	17.5 (19.14)	9.79
Tmax (h)	1.2 (47%)	1.85 (31.42)	
AUC (0-96h) (ng.h/ml)	371 (36%)	321.82 (11.68)	17.74
AUC (0-inf) (ng.h/ml)	397 (36%)	305.19 (10.9)	18.94

* patent-WO2007050377A1

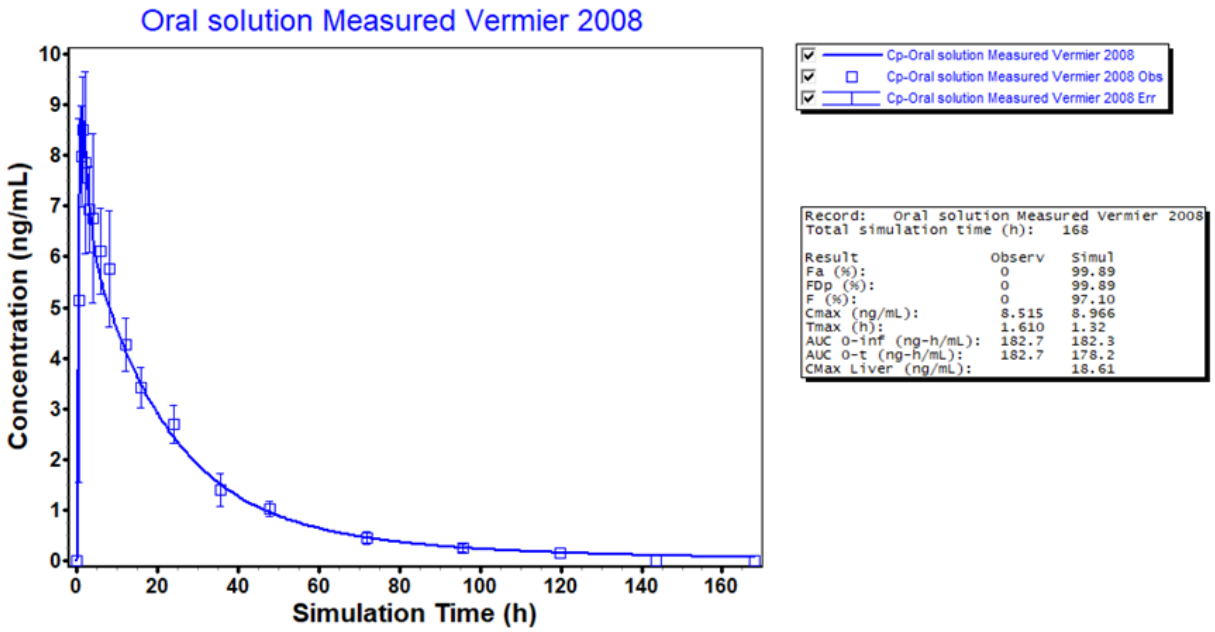
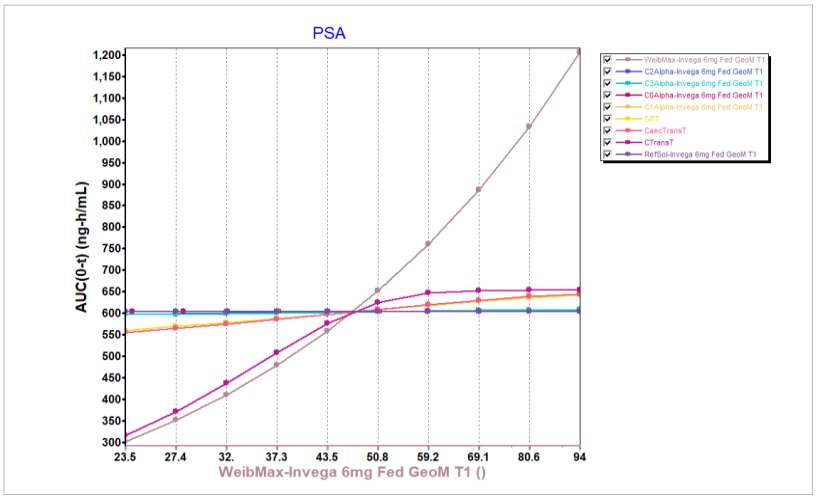


Figure S1. Predicted versus observed PAL plasma concentrations over time after the oral administration of 1 mg oral solution using the final model (blue solid line-predicted plasma concentration, blue square box with bars- observed mean plasma concentration in clinical fasted study ± standard error).

A



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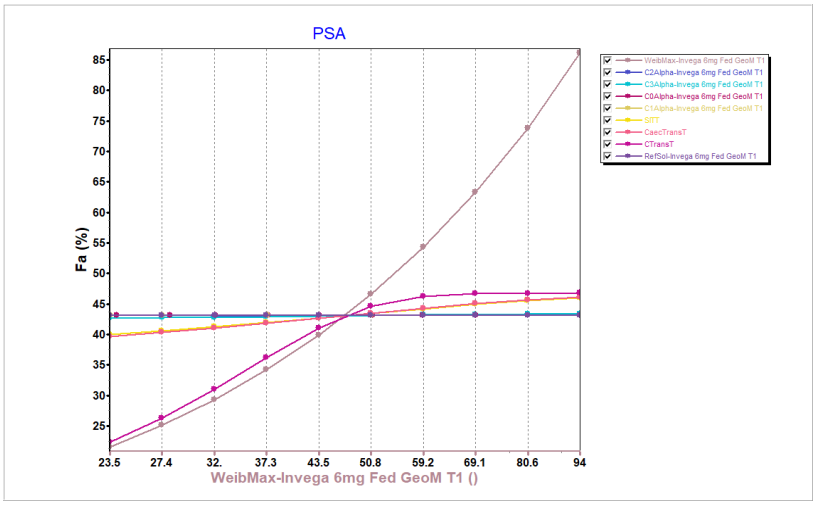


C

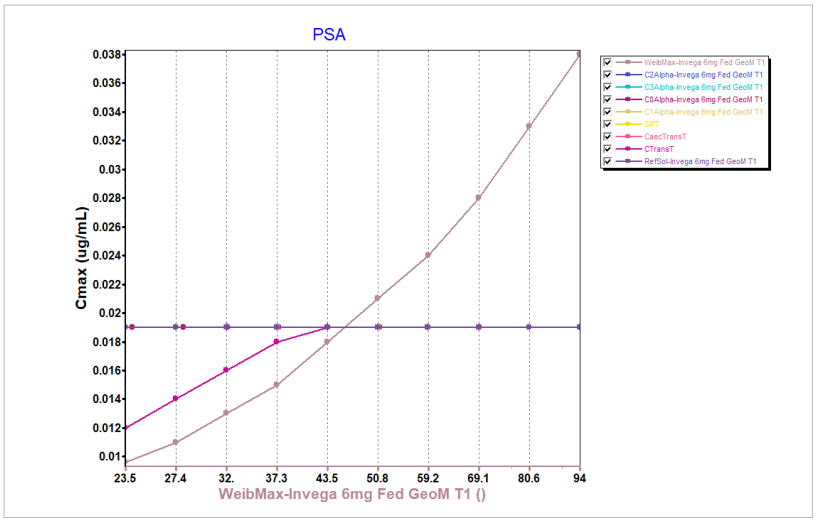


Figure S2. Parameters sensitivity analysis showing the effect of changes on different absorption-related parameters on A) the area under the curve (AUC), B) the fraction absorbed (Fa), and C) maximum plasma concentrations (Cmax).

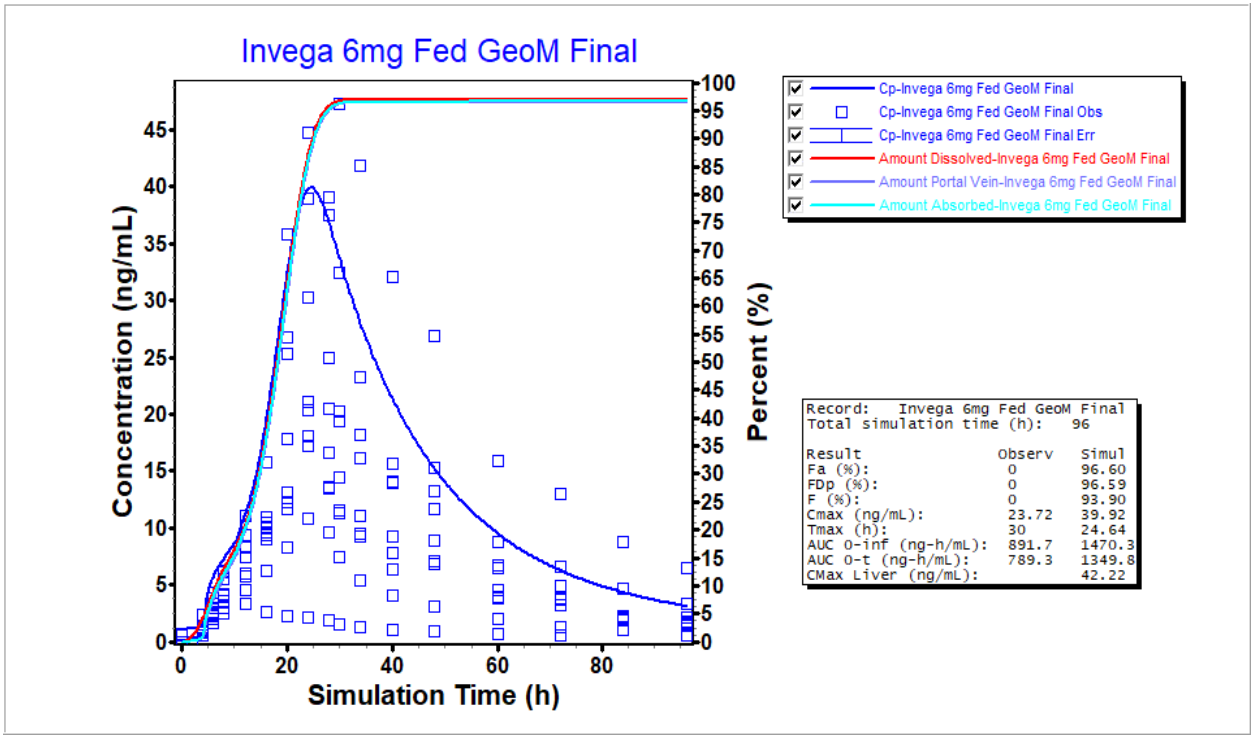
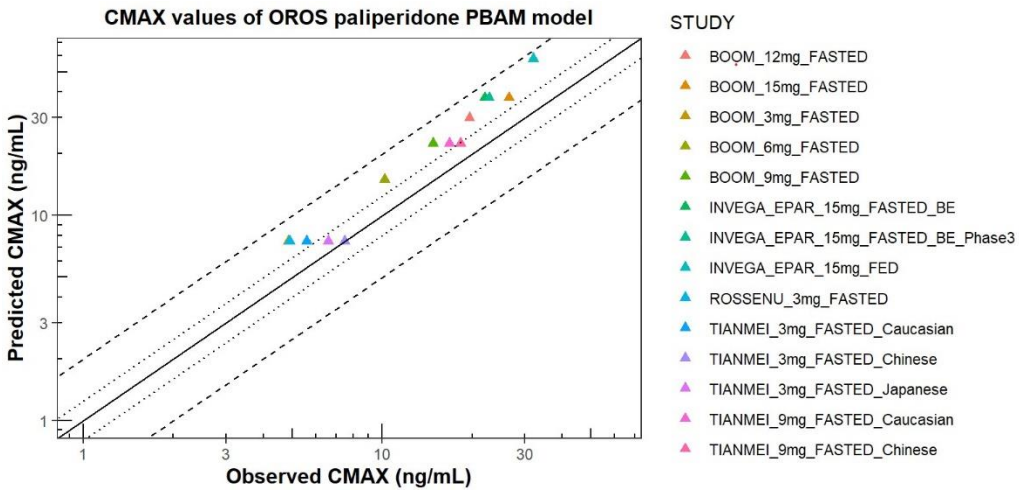


Figure S3. Simulation of the upper extreme scenario (i.e., maximum Weibull release fixed to 97% and colonic transit time fixed to 34 h) with the final model. Maximum exposure prediction with the model is not able to capture the subject with higher exposure.

A



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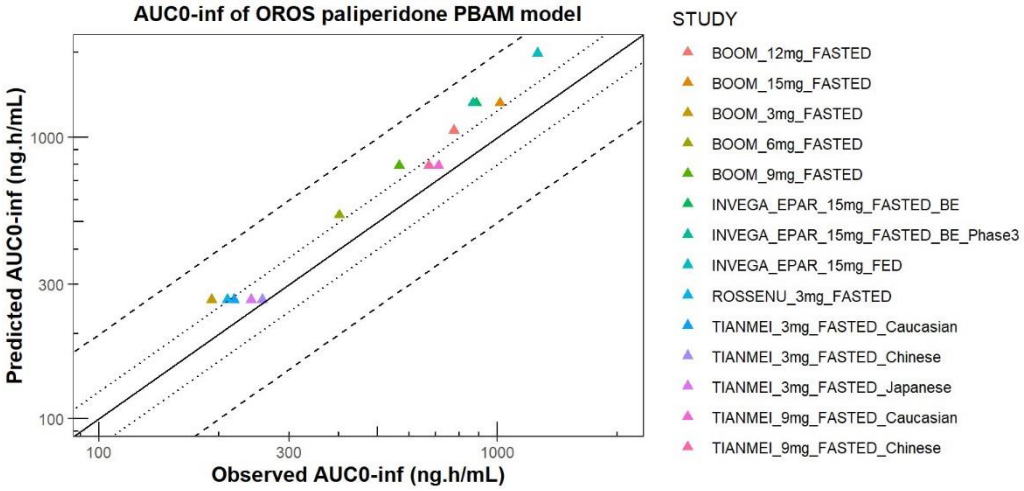

Figure S4. External validation of OROS PAL. Predicted compared to observed PAL. (A) CMAX values, (B) AUC0-inf values from all literature studies [7, 8, 9]. The line of identity is shown as a solid line; 1.25-fold deviation is shown as a dotted line; 2-fold deviation is shown as a dashed line. CMAX: maximum concentration; AUC: area under the curve.

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