Determination of Plasma Concentration Reference Ranges for Risperidone & Paliperidone

Online Supplement 2:

Population PK Models

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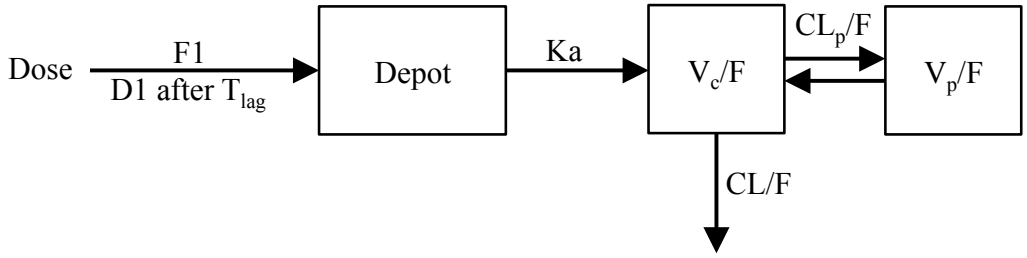
1 Population PK Model for Extended Release (ER) Oral Paliperidone

Figure S2.1: Schematic of the ER Paliperidone PK Model



CL/F = apparent clearance; CL_p/F, apparent intercompartmental flow; D1 = duration of zero-order input; F1 = apparent bioavailability (changes with occasion); Ka = absorption rate constant; T_{lag} = absorption lag time; V_c/F = apparent central volume of distribution; V_p/F = apparent peripheral volume of distribution.

Table S2.1: Parameter Estimates for the ER Paliperidone PK Model

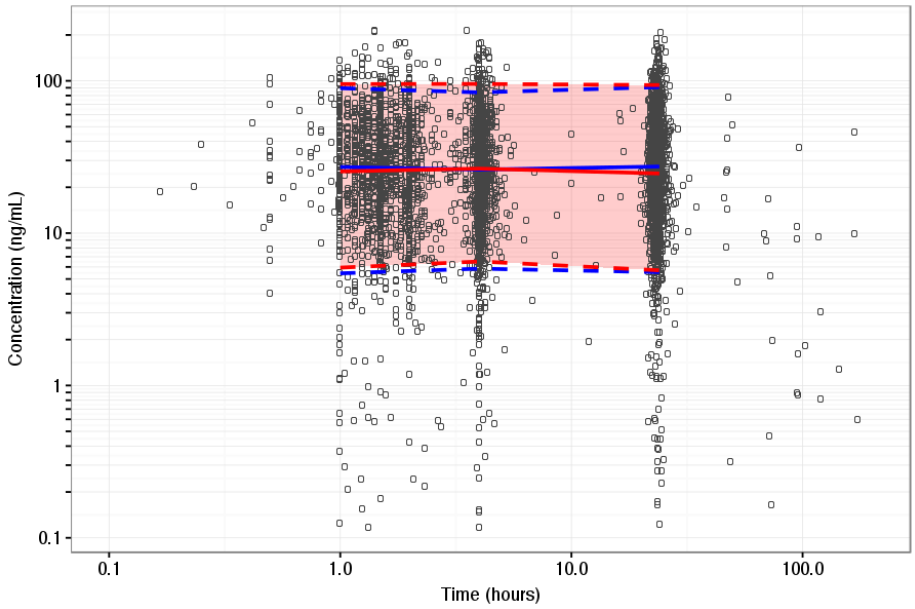
Parameter	Estimate (SE%)	BSV CV% (SE%)
Apparent clearance (CL/F, L/hr)	10.9 (11.5)	44.4 (18.1)
Effect of weight on CL/F	0.727 (21.7)	
Effect of CrCL on CL/F	0.0240 (46.3)	
Apparent intercompartmental flow (CL_p/F, L/hr)	22.0 (10.0)	
Apparent central volume of distribution (V_c/F, L)	198 (6.7)	34.5 (31.3)
Apparent peripheral volume of distribution (V_p/F, L)	244 (6.8)	28.6 (24.5)
Apparent bioavailability (F1)	1 FIX	17.4† (14.1‡)
Absorption lag time (T_{lag}, hr)	0.761 (8.7)	
Duration of input (D1, hr)	25. (0.7)	
Absorption rate constant (Ka, hr^{-1})	0.630 (2.0)	59.9 (20.3)
Residual unexplained variability (RUV, CV%)	20.5 (4.6)	

BSV = between-subject variability; CrCL = creatinine clearance; CV = coefficient of variation; SE = standard error.

*Parameterised as: $CL = \theta_1 \times (\text{weight (kg)}/74.4)^{\theta_8} + \text{CrCL (mL/min)} \times \theta_9$, where CrCL is capped at 150 mL/min.

† Between-occasion variability (BOV); ‡ SE for BOV.

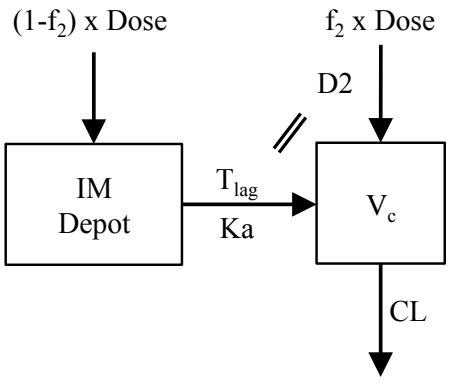
Figure S2.2: VPC for the ER Paliperidone PK Model



The blue and red lines represent the observed and simulated data, respectively; the solid lines represent the 50^{th}percentile, with the dotted lines representing the $5^{th}$and 95^{th} percentiles; while the open circles represent the observed data points.

2 Population PK Model for Long-acting Intramuscular (i.m.) Injectable (LAI) of Paliperidone

Figure S2.3: Schematic of the LAI Paliperidone PK Model



CL = clearance; D2 = duration of zero-order input into Vc (equal to Tlag); f2 = fraction of dose into V_c; IM = intramuscular; T_{lag} = absorption lag time; V_c = central volume of distribution.

Table S2.2: Parameter Estimates for the LAI Paliperidone PK Model

Parameter	Estimate (SE%)	BSV CV% (SE%)	BOV CV% (SE%)
Clearance[a] (CL, L/hr)	4.95 (1.3)	40.0 (1.8)	26.0 (2.2)
Effect of CrCL on CL	0.376 (2.7)		
Volume of distribution[b] (V_c, L)	391 (3.0)	69.0 (4.3)	14.0 (2.1)
Effect of BMI on V_c	0.889 (0.8)		
Shift factor for females	0.726 (7.5)		
Absorption rate constant $\times 10^{3,c}$ (Ka, hr^{-1})	0.488 (2.0)	59.0 (3.2)	
Effect of age on Ka	0.311 (14.0)		
Effect of injection volume	-0.359 (3.1)		
Shift factor for females	0.765 (7.4)		
Shift factor for deltoid muscle injection	1.23 (3.4)		
Duration of input (D2, hr) or absorption lagtime (T_{lag}, hr)	319 (0.6)		
Fraction of dose into V_c[d] (f_2)	0.168 (2.1)	0.064† (2.0)	0.07 † (2.2)
Effect of BMI on f_2	-0.642 (1.0)		
Effect of injection volume	-0.288 (1.2)		
Shift factor for females	0.781 (4.1)		
Shift factor for deltoid muscle injection	1.37 (3.2)		
Shift factor for deltoid muscle 1.5 inch needle	1.54 (6.0)		
Proportional residual unexplained variability (RUV, CV%)	22.0 (2.8)		

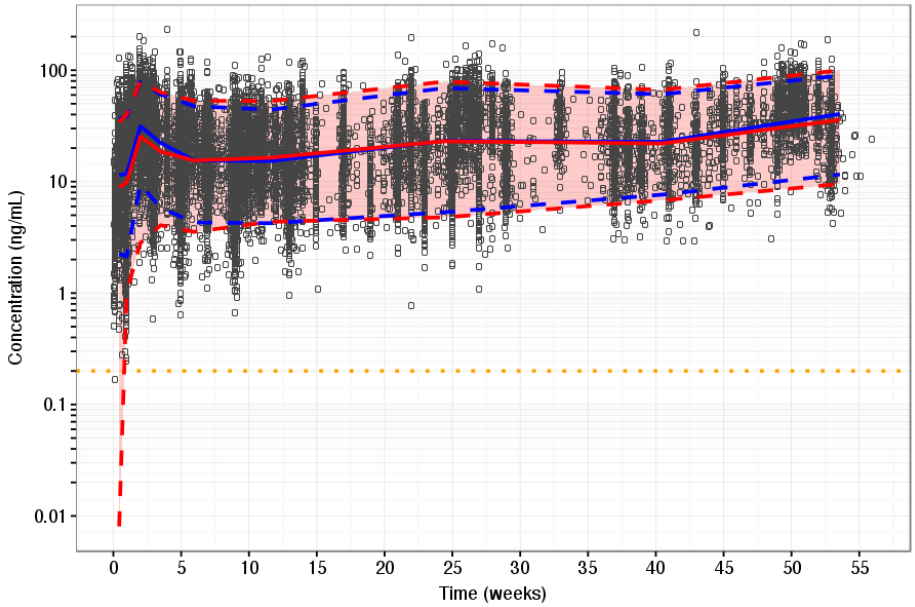
BMI = body mass index; BOV = between-occasion variability; BSV = between-subject variability; CrCL = creatinine clearance; CV = coefficient of variation; SE = standard error. † Standard deviation computed for paliperidone palmitate 100 mg eq. gluteal muscle injection for a male subject with a BMI of 26.8 kg/m^2.

[a] $CL = 4.95 \times (CrCL\ (mL/min)/110.6)^{0.376}$. [b] $V_c = 391 \times (BMI\ (kg/m^2)/26.8)^{0.889} \times 0.726$ if female.

[c] $Ka = 0.488 \times 10^{-3} \times (Age\ (yrs)/42)^{0.311} \times$ injection volume $(mL)^{-0.359} \times 0.765$ if female $\times 1.23$ if deltoid injection.

[d] $f_2 = 0.168 \times (BMI\ (kg/m^2)/26.8)^{-0.642} \times$ injection volume $(mL)^{-0.288} \times 0.781$ if female $\times 1.37$ if deltoid injection $\times 1.54$ if deltoid injection with 1.5 inch needle.

Figure S2.4: VPC for the LAI Paliperidone PK Model



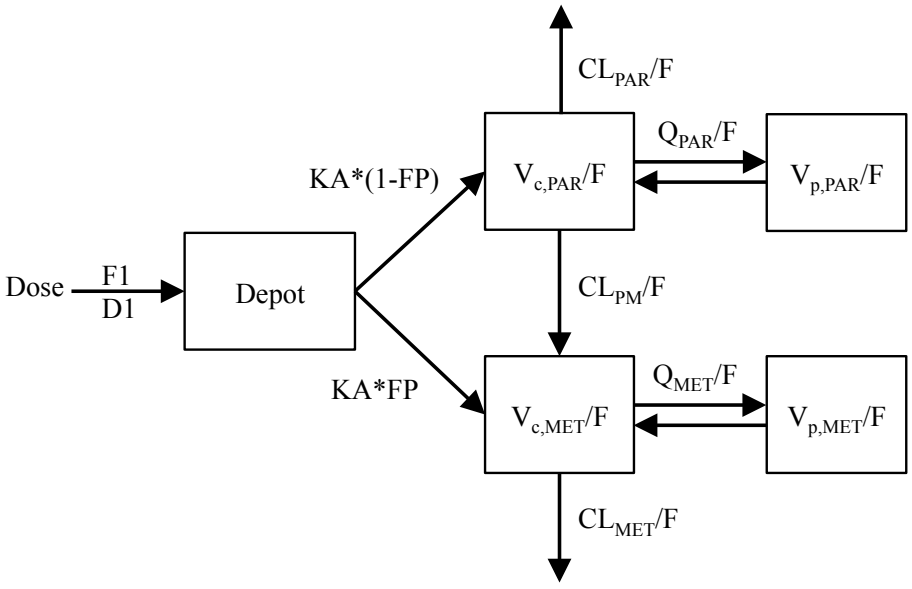
The blue and red lines represent the observed and simulated data, respectively; the solid lines represent the 50^{th}percentile, with the dashed lines representing the $5^{th}$and 95^{th} percentiles; while the open circles represent the observed data points, and the orange dotted horizontal line indicates the lower limit of quantification (LLOQ).

3 Population PK Model for Oral Risperidone

The following modifications were undertaken during the update of the population PK model for oral risperidone:

- Inclusion of an additional parameter describing the apparent clearance of risperidone for unknown concomitant administration of carbamazepine.
- A joint estimate of the apparent clearance of paliperidone in subjects where concomitant administration or absence of concomitant carbamazepine was known.
- Inclusion of an additional parameter describing the apparent clearance of paliperidone where concomitant administration of carbamazepine was unknown.
- Removal of the study effect that allowed for differing proportions of intermediate and extensive CYP2D6 metabolisers in single dose trials.
- Inclusion of age as a covariate effect on the apparent clearance of risperidone, which increased linearly to an estimated age cut-point, and declined thereafter in a non-linear manner.

Figure S2.5: Schematic of the Parent-Metabolite PK Model



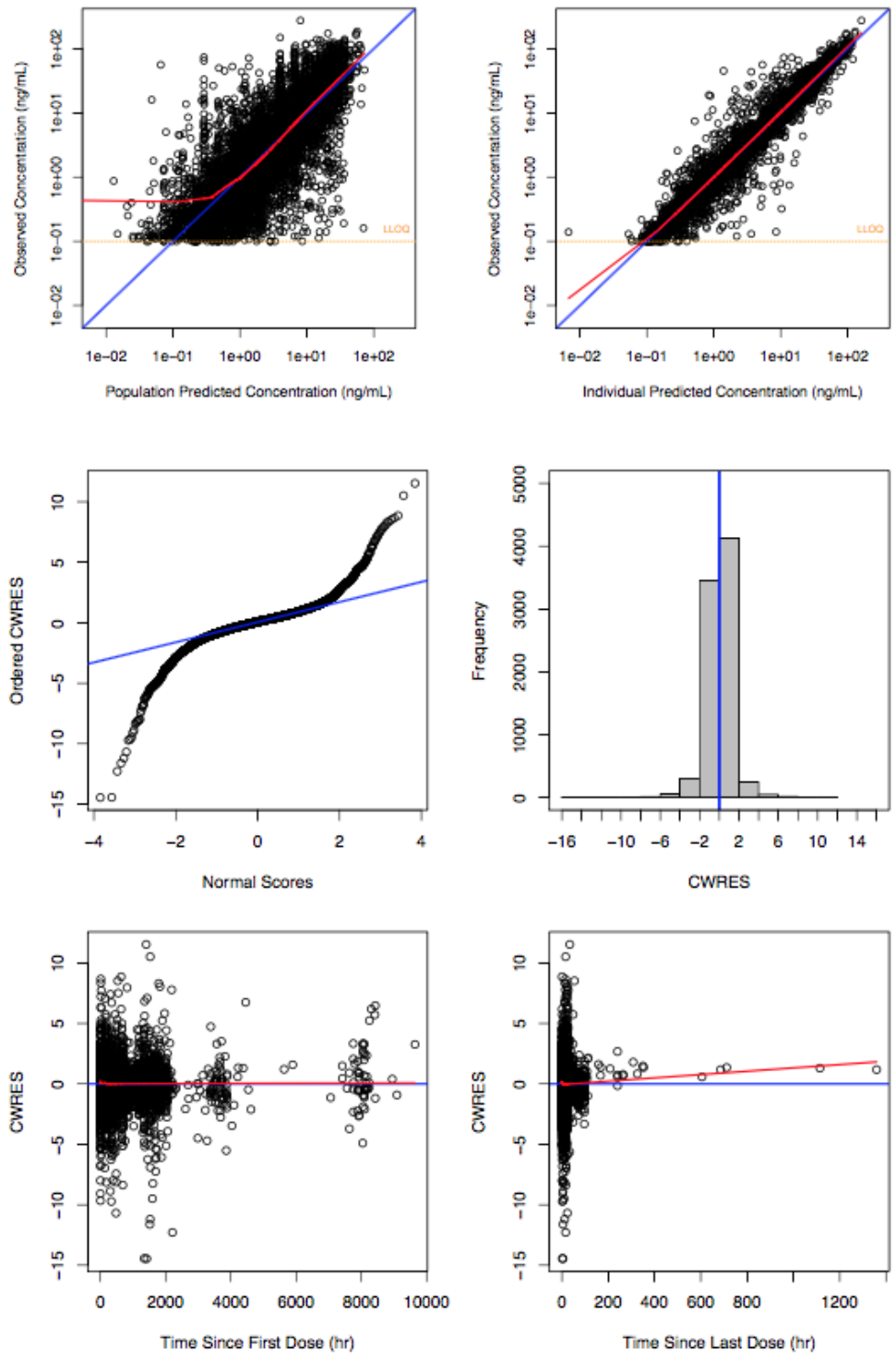
CL_{MET}/F = apparent clearance of metabolite; CL_{PAR}/F = apparent clearance of parent; CL_{PM}/F = apparent clearance from parent to metabolite; D1 = duration of zero-order input into the depot compartment; F1 = apparent bioavailability; FP = fraction of dose converted to 9-OH (first-pass metabolism); KA = absorption rate constant; Q_{MET}/F = apparent intercompartmental flow of metabolite; Q_{PAR}/F = apparent intercompartmental flow of parent; $V_{c,MET}/F$ = apparent central volume of distribution of metabolite; $V_{c,PAR}/F$ = apparent central volume of distribution of parent; $V_{p,PAR}/F$ = apparent peripheral volume of distribution of parent; $V_{p,MET}/F$ = apparent peripheral volume of distribution of metabolite.

Table S2.3: Parameter Estimates for the Parent-Metabolite PK Model

Parameter	Estimate (SE%)	BSV CV% (SE%)	BOV CV% (SE%)
Apparent bioavailability (F1)			46.9 (18.0)
Absorption lag time (ALAG1, h)	0.168 (4.9)	38.1 (35.9)	
Duration of input (D1, h)	0.447 (4.9)	71.3 (48.9)	146 (22.5)
Absorption rate constant (KA, /h)	2.01 (8.2)	91.4 (38.8)	127 (29.7)
Fraction of dose converted to paliperidone (FP, %)		102[a] (20.0)	
Poor metabolisers	3.69 (30.6)		
Intermediate metabolisers	7.10 (37.6)		
Extensive metabolisers	42.7 (5.7)		
Apparent intercompartmental flow of parent (Q_{PAR}, L/h)	2.67 (8.5)	78.0 (83.3)	
Apparent clearance of parent (CL_{PAR}, L/h)			96.3 (56.8)
No concomitant CBZ (L/h)	5.95 (18.7)		
With concomitant CBZ (L/h)	12.1 (19.8)		
Unknown concomitant CBZ (L/h)	5.63 (24.2)		
Cut point for effect of age on CL_{PAR}	23.2 (12.3)		
Effect of age on CL_{PAR}	-0.769 (34.3)		
Apparent clearance from parent to metabolite (CL_{PM}, L/h)		42.9 (12.8)	
Poor metabolisers	1.47 (15.5)		
Intermediate metabolisers	9.01 (15.4)		
Extensive metabolisers	17.5 (7.0)		
Apparent central volume of distribution of parent ($V_{c,PAR}$, L)	113 (4.2)	21.0 (40.5)	
Apparent peripheral volume of distribution of parent ($V_{p,PAR}$ (L)	71.9 (13.8)	50.0 (68.0)	
Apparent intercompartmental flow of metabolite (Q_{MET}, L/h)	1.54 (8.4)	0 FIXED	
Apparent clearance of metabolite (CL_{MET}, L/h)		16.5 (31.9)	
Known concomitant CBZ (L/h)	5.50 (3.5)		
Unknown concomitant CBZ (L/h)	4.94 (5.4)		
Apparent central volume of distribution of metabolite ($V_{c,MET}$, L)*	113 (4.2)	21.0 (40.5)	
Apparent peripheral volume of distribution of metabolite ($V_{p,MET}$, L)	83.3 (9.9)	56.7 (64.5)	
Mixture for metabolising status (%)			
Poor metabolisers	9.63 (18.4)		
Intermediate metabolisers	23.0 (22.3)		
Extensive metabolisers	67.4		
Proportional residual unexplained variability for risperidone (CV%)	29.5 (11.7)		
Proportional residual unexplained variability for paliperidone (CV%)	31.1 (10.7)		

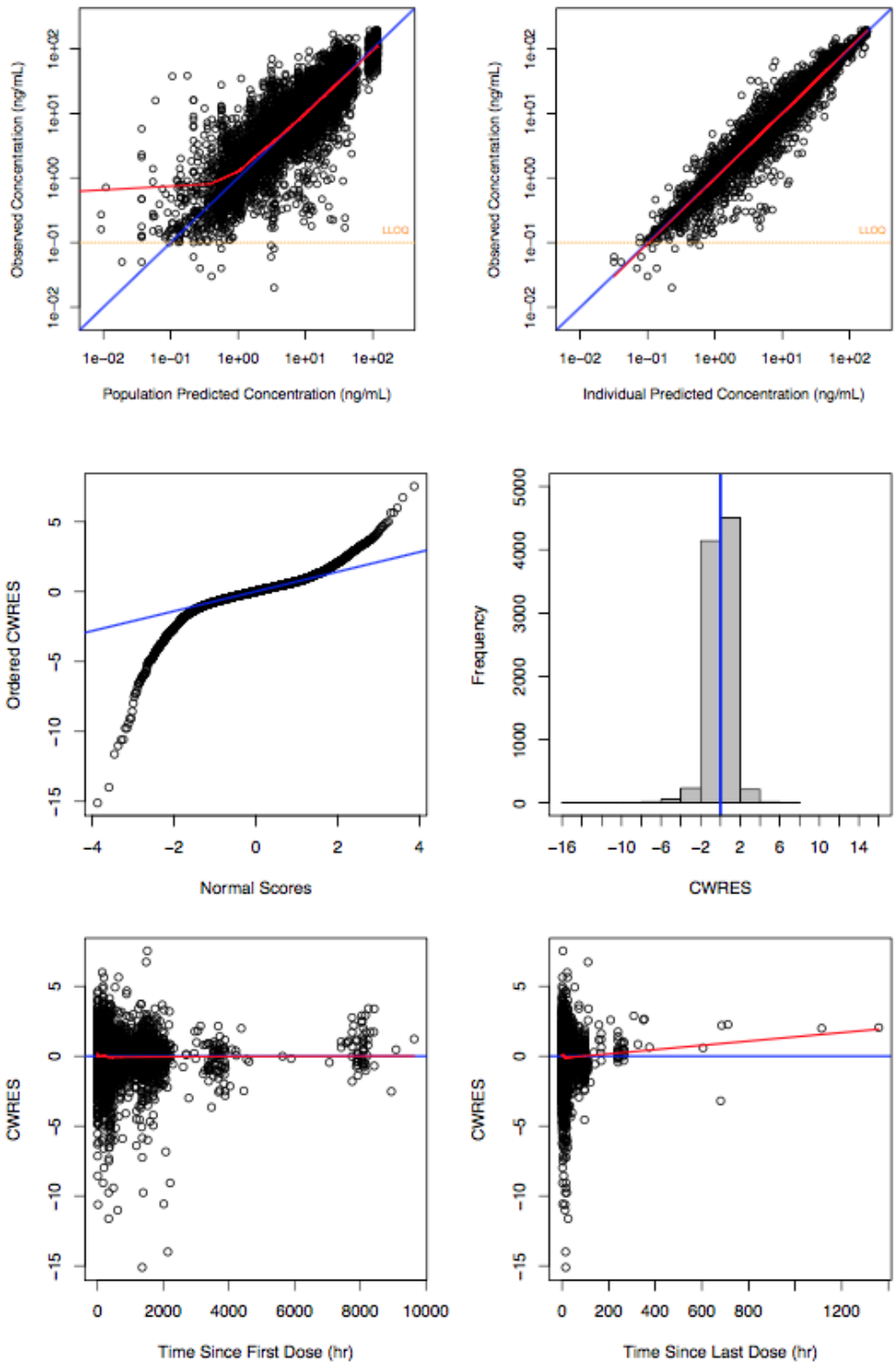
BOV = between-occasion variability; BSV = between-subject variability; CV = coefficient of variation; CBZ = carbamazepine; SE = standard error. *Same as $V_{c,PAR}$, [a]%SD in the logit domain.

Figure S2.6: Goodness-of-fit Plots for Risperidone – Evaluation Dataset



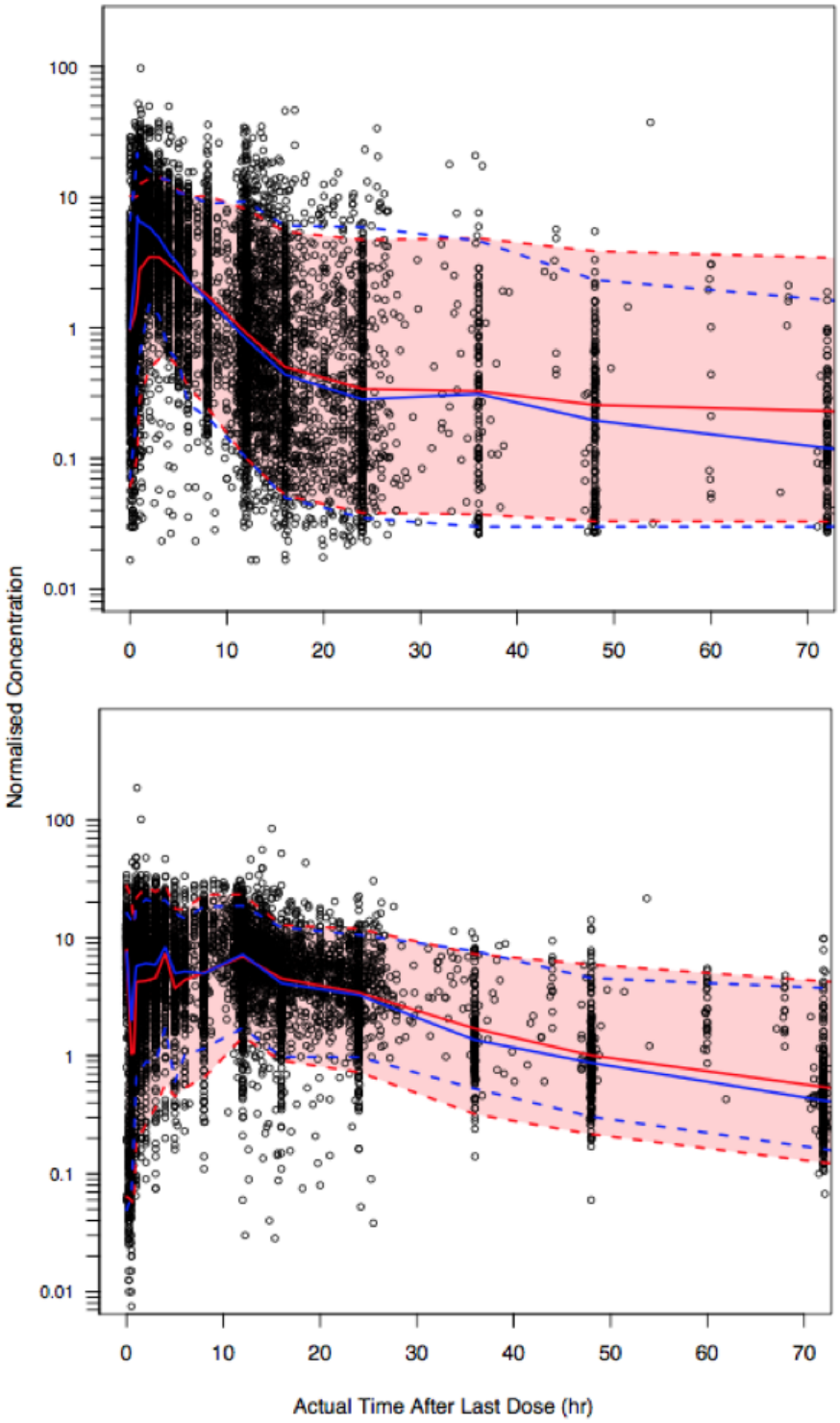
The blue solid lines represent the expected trend, the solid red lines represent the trend of the data, and the orange horizontal lines indicate the LLOQ; CWRES = conditional weighted residuals.

Figure S2.7: Goodness-of-fit Plots for Paliperidone – Evaluation Dataset



The blue solid lines represent the expected trend, the solid red lines represent the trend of the data, and the orange horizontal lines indicated the LLOQ; CWRES = conditional weighted residuals.

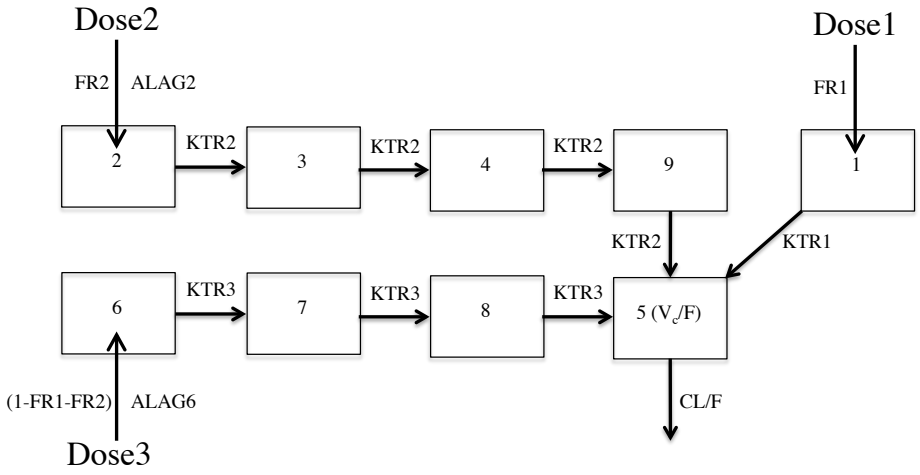
Figure S2.8: VPCs for Risperidone (top) & Paliperidone (bottom) – Evaluation Dataset



The blue and red lines represent the observed and simulated data, respectively; the solid lines represent the 50^{th} percentiles, with the dashed lines representing the $5^{th}$and 95^{th} percentiles; the open circles represent the observed data points colour-coded by study; and the orange horizontal lines indicated the LLOQ.

4 Population PK Model for the Active Moiety of i.m. Risperidone Administered as LAI

Figure S2.9: Schematic of the PK Model for the Active Moiety of i.m. LAI Risperidone



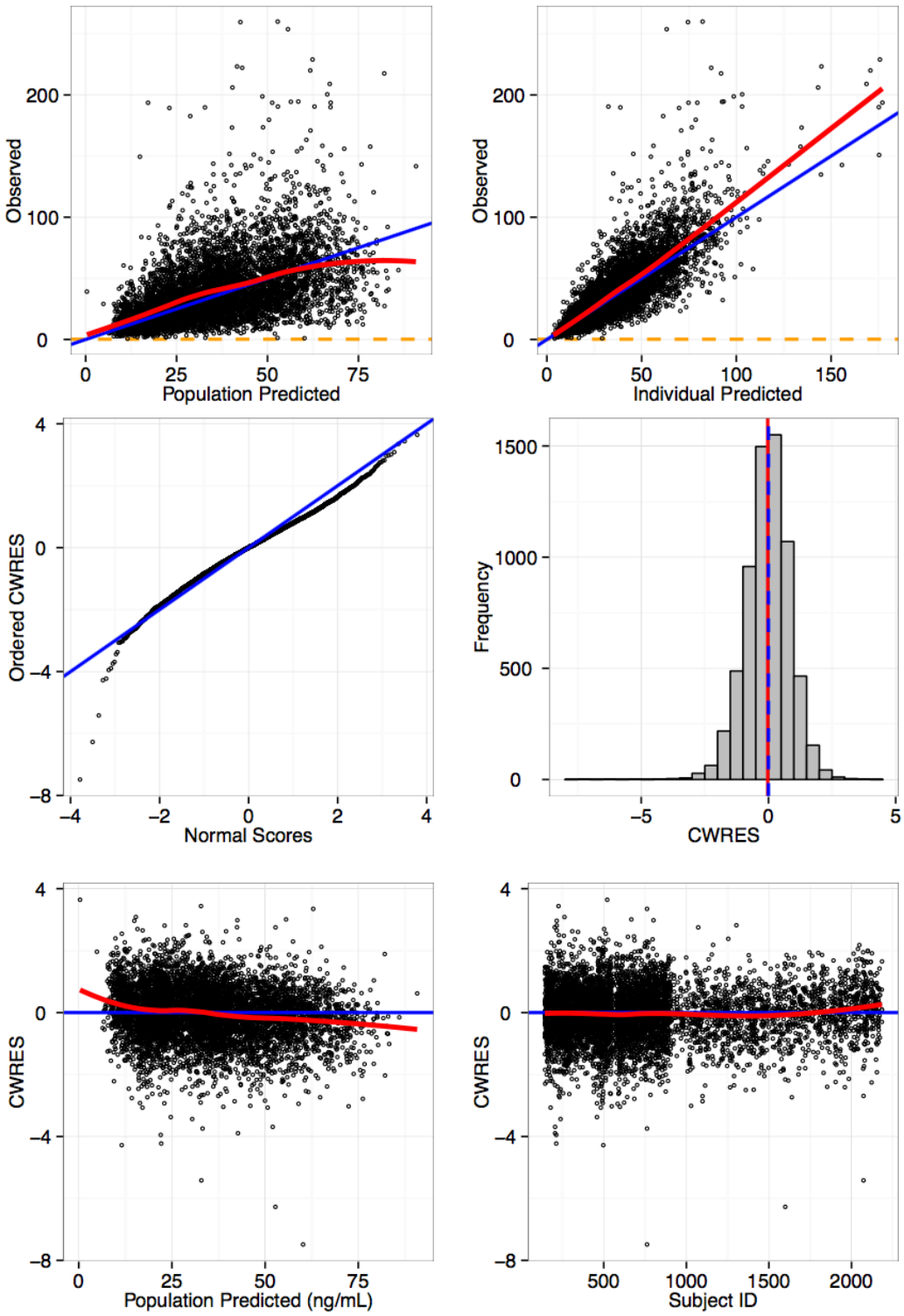
ALAG2 = absorption lagtime of the second pathway; ALAG6 = absorption lagtime of the third pathway; CL/F = apparent clearance; F = apparent bioavailability; FR1 = fraction of dose absorbed via the first pathway; FR2 = fraction of dose absorbed via the second pathway; KTR1 = first-order absorption rate constant of the first pathway; KTR2 = transit absorption rate constant of the second pathway; KTR3 = transit absorption rate constant of the third pathway; V_c/F = apparent central volume of distribution.

Table S2.4: Parameter Estimates for the Active Moiety of i.m. LAI Risperidone

Parameter	Estimate (SE%)	BSV CV% (SE%)	BOV CV% (SE%)
Apparent Clearance (CL/F, L/hr)	4.27 (8.0)	39.1 (7.88)	
Effect of LBW on CL/F	0.725 (32.3)		
Apparent Central Volume of Distribution (V_c/F, L)	351 (3.48)		
First-order Absorption Rate Constant (KTR1, hr^{-1})	100 FIX (NA)		
Absorption Transit Rate Constant 2 (KTR2, hr^{-1})	0.00730 (5.06)	66.7 (15.5)	
Absorption Transit Rate Constant 3 (KTR3, hr^{-1})	0.0177 (4.63)		41.5 (11.3)
Fraction of Dose via Pathway 1 (FR1, %)#	3.21 (3.74)	32.1 (21.4)^{B3}	
Fraction of Dose via Pathway 2 (FR2, %)#	21.7 (8.96)	82.4 (10.5)^{B1}	
		46.4 (17.5)^{B3}	
Effect of Formulation Batch 3 on FR2*	3.56 (15.1)		
Fraction of Dose via Pathway 3 ((1-FR2-FR1), %)	75.09 (NA)		
Lag-time for Pathway 2 (ALAG2, hr)	0 FIX (NA)		
Lag-time for Pathway 3 (ALAG6, hr)	613 (0.45)		
Residual unexplained variability for Batch 1 (RUV, CV%)	28.4 (2.87)		
Residual unexplained variability for Batch 3 (RUV, CV%)	47.4 (3.22)		

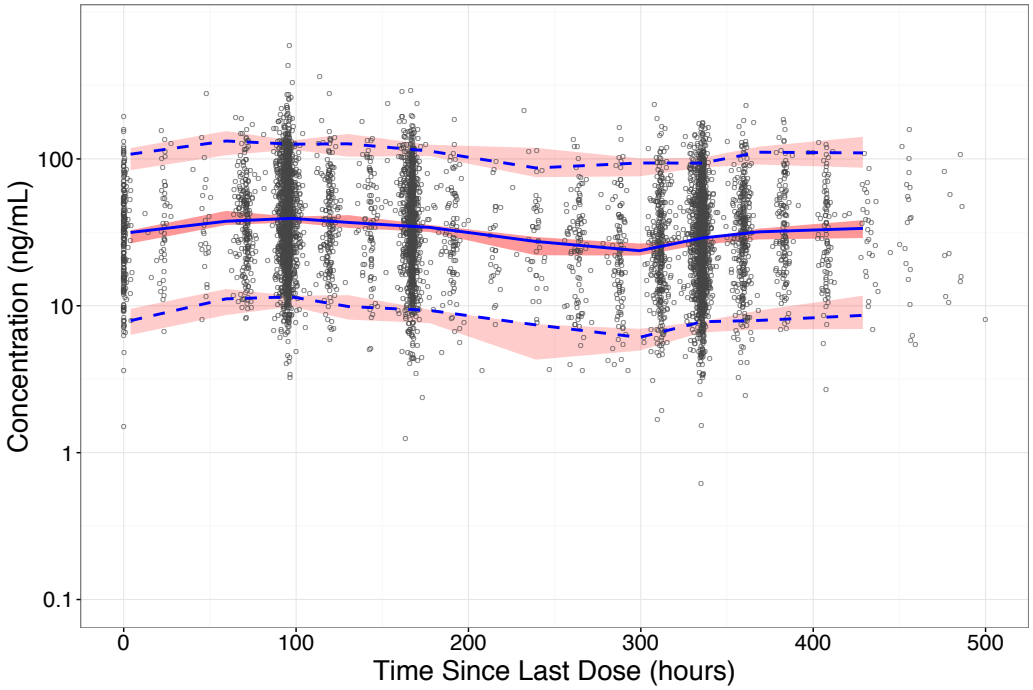
B1 = Batch 1; B3 = Batch 3; BSV = between Subject Variability; BOV = between-occasion variability; CV = coefficient of variation; LBW = lean body weight; SE = standard error. # = parameter converted out of a logit domain for ease of interpretation; * = represents an increase in FR2 to 49.1% when converted out of a logit.

Figure S2.10: Goodness-of-fit Plots for the Active Moiety of i.m. LAI Risperidone – Evaluation Dataset



The blue solid lines represent the expected trend, the solid red lines represent the trend of the data, and the orange horizontal lines indicate the LLOQ; CWRES = conditional weighted residuals.

Figure S2.11: VPC for the Active Moiety of i.m. LAI Risperidone – Evaluation Dataset



The blue lines represent the observed data, where the solid line represents the 50^{th}percentile, with the dashed lines representing the $5^{th}$and 95^{th} percentiles; the red shaded areas represent the corresponding 95%CIs for the simulated data; and the open circles represent the observed data points.