ONLINE RESOURCE

Clinical Pharmacokinetics

Title: **Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase 2 and Phase 3 Trials**

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Table S1 Genotype Distribution in Phase 3 Efficacy Study (Study 2) for CYP450 and UGT enzymes

Characteristics	Level	300/100 mg	300/300 mg	Placebo
CYP2C8*3 (rs10509681) (N(%))	CC	1 (0.5)	2 (1.0)	0 (0.0)
	TC	23 (11.9)	33 (16.8)	14 (14.1)
	TT	160 (82.5)	147 (75.0)	81 (81.8)
	Missing	10 (5.2)	14 (7.1)	4 (4.0)
CYP3A4*22 (rs35599367) (N(%))	AA	0 (0.0)	1 (0.5)	0 (0.0)
	GA	9 (4.6)	13 (6.6)	6 (6.1)
	GG	175 (90.2)	169 (86.2)	89 (89.9)
	Missing	10 (5.2)	13 (6.6)	4 (4.0)
CYP3A4*2 (rs55785340) (N(%))	AA	183 (94.3)	183 (94.3)	95 (96.0)
	GA	1 (0.5)	0 (0.0)	0 (0.0)
	Missing	10 (5.2)	13 (6.6)	4 (4.0)
CYP3A4*1B (rs2740574) (N(%))	CC	25 (12.9)	26 (13.3)	6 (6.1)
	TC	36 (18.6)	32 (16.3)	12 (12.1)
	TT	122 (62.9)	124 (63.3)	76 (76.8)
	Missing	11 (5.7)	14 (7.1)	5 (5.1)
UGT2B7*3 (rs12233719) (N(%))	GG	184 (94.8)	183 (93.4)	95 (96.0)
	Missing	10 (5.2)	13 (6.6)	4 (4.0)
UGT1A1 (rs8175347) (N(%))	TA5TA5	0 (0.0)	1 (0.5)	0 (0.0)
	TA5TA6	1 (0.5)	3 (1.5)	3 (3.0)
	TA5TA7	2 (1.0)	0 (0.0)	1 (1.0)
	TA5TA8	1 (0.5)	1 (0.5)	0 (0.0)
	TA6TA6	73 (37.6)	77 (39.3)	42 (42.4)
	TA6TA7	79 (40.7)	70 (35.7)	39 (39.4)
	TA6TA8	2 (1.0)	2 (1.0)	1 (1.0)
	TA7TA7	24 (12.4)	24 (12.2)	10 (10.1)
	TA7TA8	1 (0.5)	4 (2.0)	0 (0.0)
	Missing	11 (5.7)	14 (7.1)	3 (3.0)

Table S2 Parameter Estimates of Population Pharmacokinetic Model at Each Step of Model Development

Para-meter	Description	Step 1 (Study 1)			Step 2 (Studies 1+2)			Step 3 (Studies 1+2+3)		
		Estimate (%RSE)	Variance (%RSE)	%CV	Estimate (%RSE)	Variance (%RSE)	%CV	Estimate (%RSE)	Variance (%RSE)	%CV
CL/F	BUP-XR apparent elimination clearance (L/hr)	51.7 (1.4)	0.167 (9.4)	43	49.8 (2.8)	0.121 (16)	35.9	52.0 (1.5)	0.0871 (9.5)	30.2
V4/F	BUP-XR apparent volume of central compartment (L)	362 (1.3)	0.366 (7.5)	66	462 (7.4)	0.775 (40)	108	433 (27)	0.647 (12)	95.4
Q/F	BUP-XR apparent distribution clearance (L/hr)	79.5 (1.6)	0.334 (9.2)	63	79.5 (FIXED)	0.334 (FIXED)	62.9	79.5 (FIXED)	0.334 (FIXED)	63.0
V5 (L)	BUP-XR apparent volume of peripheral compartment (L)	1110 (1.6)	0.941 (13)	125	1110 (FIXED)	0.941 (FIXED)	125	1110 (FIXED)	0.941 (FIXED)	125
k14	SL absorption rate constant (1/hr)	1.17 (33)	0.190 (0.36)	46	1.17 (FIXED)	0.190 (FIXED)	45.7	1.17 (FIXED)	0.190 (FIXED)	45.7
k24	Fast absorption rate constant from SC depot (1/hr)	0.0181 (1.6)	0.307 (15)	60	0.0294 (9.9)	0.758 (41)	107	0.0276 (5.1)	0.654 (16)	96.1
k36	Slow absorption rate constant from SC depot (1/hr)	0.00333 (1.9)	0.658 (14)	97	0.00370 (8.3)	1.65 (13)	205	0.00362 (7.4)	1.54 (11)	191
k64	Rate constant from Transit to Central compartments (1/hr)	0.000433 (1.1)	0.317 (15)	61	0.000483 (5.4)	0.580 (12)	88.6	0.000510 (3.7)	0.432 (11)	73.5
F1	Relative bioavailability for SL buprenorphine tablets vs. BUP-XR	0.185 (4.3)	0.195 (12)	46	0.185 (FIXED)	0.195 (FIXED)	46.4	0.185 (FIXED)	0.195 (FIXED)	46.4
F2	Fraction of SC dose absorbed by fast process	0.0612 (2.1)	0.169 (1.0)	NA[a]	0.0661 (2.8)	0.223 (13)	NA[a]	0.0679 (2.2)	0.204 (11)	NA[a]
FRK14	Relative change in k14 for film vs tablet formulation	NA	NA	NA	0.898 (28)	NA	NA	0.650 (11)	NA	NA
FRF1	Relative change in F1 for film	NA	NA	NA	1.37 (9.1)	NA	NA	1.47 (3.5)	NA	NA

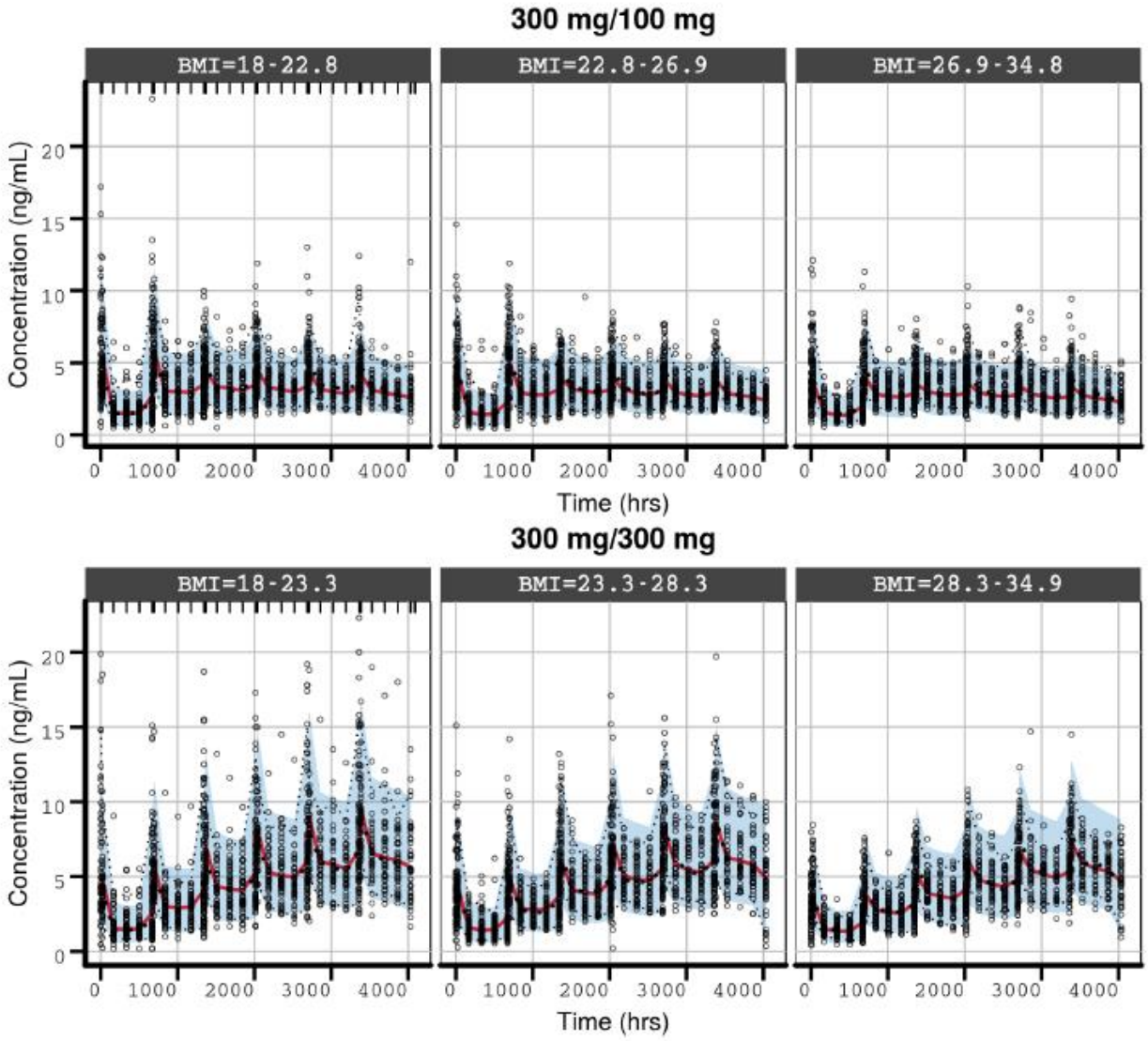
Para-meter	Description	Step 1 (Study 1)			Step 2 (Studies 1+2)			Step 3 (Studies 1+2+3)		
		Estimate (%RSE)	**Variance (%RSE)**	**%CV**	**Estimate (%RSE)**	**Variance (%RSE)**	**%CV**	**Estimate (%RSE)**	**Variance (%RSE)**	**%CV**
	vs tablet formulation									
F1DOSE	Relative change in F1 for dose ≥16mg compared to <16mg	0.674 (41)	NA	NA	0.765 (36)	NA	NA	0.765 (FIXED[b])	NA	NA
θ_{BMI} (CL)	Power coefficient for BMI on CL/F	NA	NA	NA	-0.408 (21)	NA	NA	-0.364 (21)	NA	NA
θ_{BMI} (k24)	Power coefficient for BMI on k24	NA	NA	NA	-1.29 (15)	NA	NA	-1.32 (14)	NA	NA
θ_{SEX} (k36)	Fractional increase in k36 for females	NA	NA	NA	0.0759 (140)	NA	NA	0.0313 (282)	NA	NA
		Residual Variability (%RSE)								
PROP	Proportional residual error	0.179 (0.52)			0.190 (0.97)			0.190 (0.66)		
ADD	Additive residual error (ng/mL)	0.01 (FIXED)			0.0378 (14)			0.0373 (14)		

[a] logit-normal distribution

[b] fixed, given extremely sparse SL data in Study 3 (1 sample taken prior to BUP-XR Injection 1)

BMI=body mass index; CV=coefficient of variation for log-normal distribution calculated as $100 \times \sqrt{\exp(\omega^2) - 1}$, where ω^2 is the variance of the random effect; NA=not applicable; RSE=relative standard error; SC=subcutaneous; SL=sublingual

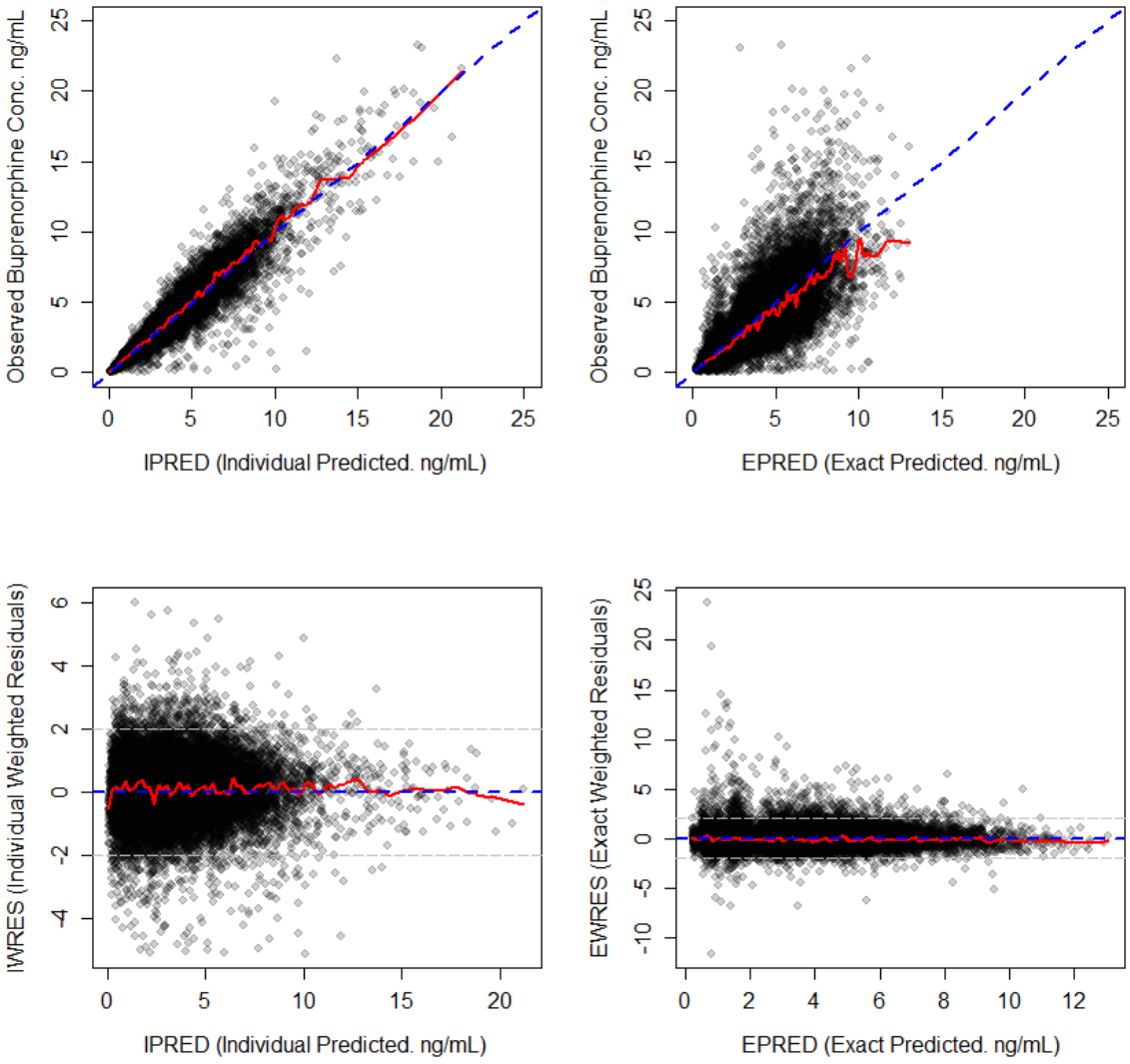
Figure S1 Effect of Body Mass Index (BMI) on Buprenorphine Plasma Exposure Following BUP-XR Administration in the Phase 3 Efficacy Study (Study 2)



Dots: observed data; Black bold dotted curve: observed medians; Black dotted curves: observed 5th and 95th percentiles

Red curve: medians of the simulated data; Shaded blue area: 90% prediction intervals of the simulated data;

Figure S2 Standard Diagnostic Plots for Final Population Pharmacokinetic Model



Upper panels: the blue dashed line represents the line of unity. Lower panels: grey and blue dashed lines are reference lines. Red lines are tendency curves through the data.