Supplemental Table 1, Genetic polymorphisms considered in the current study.

Gene	dbSNP	mRNA location	Amino acid change	TaqMan Assay ID	Minor allele frequency in the current study		
					Total	CA[1)]	AA[2)]
OCT1	rs12208357	286C>T	Arg61Cys	C__30634096_10	0.051	0.058	0.036
OCT1	rs34130495	1306G>A	Gly401Ser	Custom-made[3)]	0.034	0.044	0.000
OCT1	rs72552763	1365GAT>del	Met420del	C__34211613_10	0.154	0.164	0.089
OCT1	rs34059508	1498G>C	Gly465Arg	C__30634080_20	0.027	0.027	0.018
OCT1	rs622342	A>C	-	C_928527_20	0.315	0.327	0.250
UGT2B7[4)]	rs7438135	-900 A>G	-	C__26058102_10	0.462	0.500	0.304

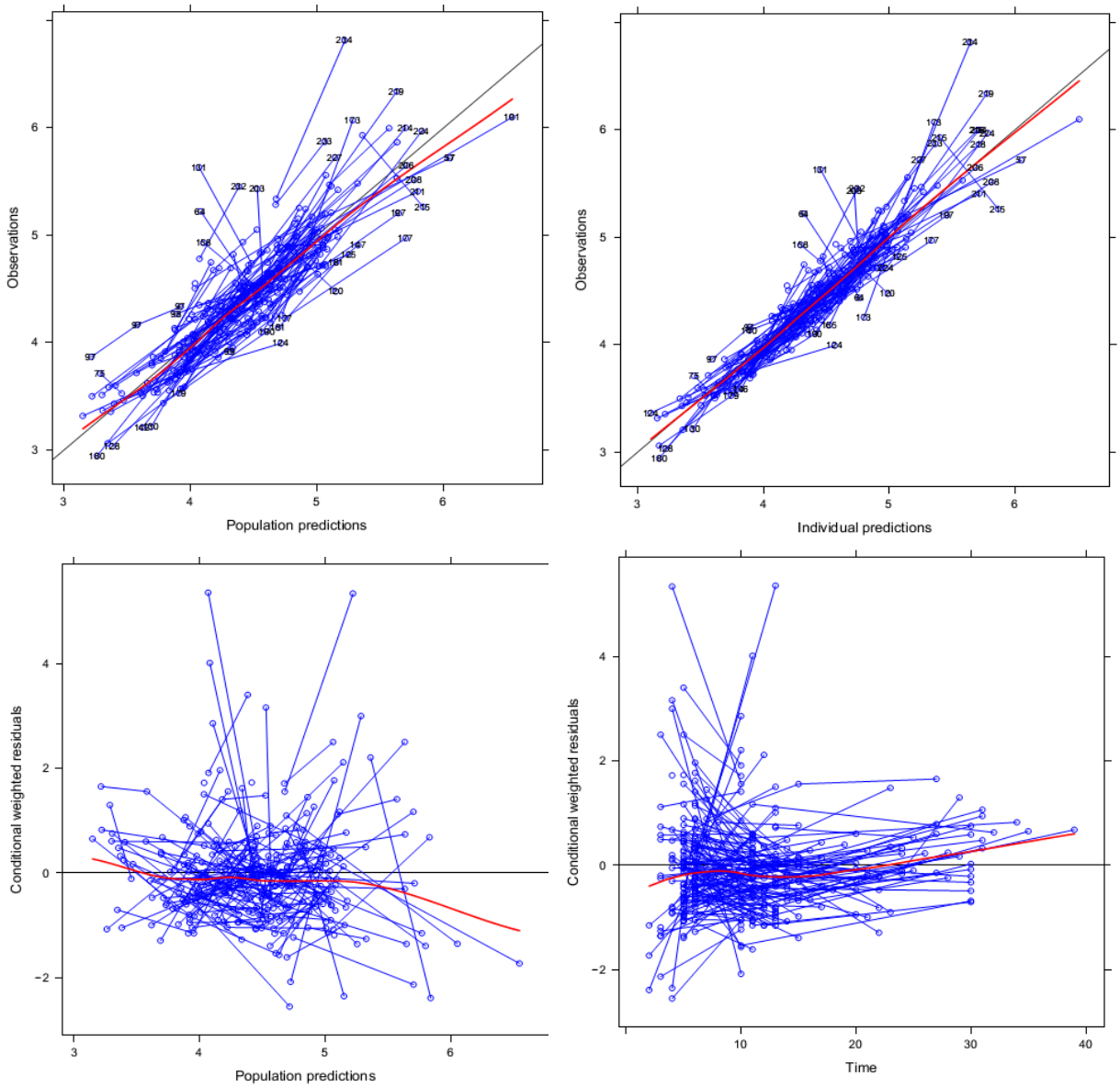
Note:

1) Caucasians
2) African Americans
3) TaqMan probe and primer designs were as follows: forward primer (TTCATAGCCCTCATCACCATTGAC) and reverse primer (CCCCGCCAACAAATTTGACATG), FAM-probe (CGCGTGAGCCGCA), and VIC-probe (CGCGTGGGCCGCA). The two clusters appeared in a TaqMan discrimination plot for patients heterozygous for the 1306G>A allele (rs34130495) maybe due to reverse primer sequence which was designed on a region of one SNP (rs628031), not a target SNP in the present study. To clarify the TaqMan results, direct sequencing was performed for all patients who were genotyped as heterozygous or homozygous for the 1306A allele and 11 wild-type patients. We confirmed that all genotyping results for 1306G>A allele (rs34130495) were the same and the two clusters were based on presence or absence of SNP (rs628031). The primer sequences for direct sequencing were as follows: forward primer (TTTCTTCAGTCTCTGACTCATGCC) and reverse prime (AAAAAACTTTGTAGACAAAGGTAGCACC). The sequencing was carried out using forward primer for amplification.
4) The SNP (rs7438135) was different from the two SNPs tested in our previous study (rs7668258 , -161T>C and rs7439366, 802T>C), but was found to be completely linked with the two SNPs.

Supplement Table 2, Model building process

No	Base	Description	Est. Succ ?	Cov. Step Succ ?	OFV	dOFV	Comments
1		2-Compartment base model without IIV	y	n	-183.3		
2	1	Base Model + IIV on CL (Base Model 2)	y	y	-344.1	-160.8	PK variation explained best by IIV on CL
3	1	Base Model + IIV on V1	y	n	-277.3	-93.99	
4	1	Base Model + IIV on Q	y	y	-290.2	-106.9	
5	1	Base Model + IIV on V2	y	y	-327.7	-144.4	
6	2	Base Model 2 + OCT effect on CL	y	y	-350.3	-6.2	Effect of OCT is significant in the base model
7	2	Base Model 2 + Allometric scaling parameters estimated for CL, V1, Q and V2	y	y	-485.5	-141.4	Significant effect of including WT as a covariate
8	7	Base Model 2 + OCT effect on CL + Allometric scaling parameters estimated for CL, V1, Q and V2	y	y	-491.4	-5.9	Effect of OCT is significant in the allometric WT model.
9	2	Base Model 2 + Allometric scaling parameters FIXED for CL, V1, Q and V2	y	y	-463.4	-119.3	Significant effect of including WT as a covariate (Allometric scaling parameters fixed)
10	9	Base Model 2 + OCT effect of on CL + Allometric scaling parameters FIXED for CL, V1, Q and V2	y	y	-468.6	-5.2	Effect of OCT is significant in the allometric WT model.
11	7	Base Model 2 + IIV on V1 + Allometric scaling parameters estimated for CL, V1, Q and V2	y	y	-501.9	-16.4	The Epsilon shrinkage and Eta shrinkage for V1 were > 30 % and uncertainty in multiple population model parameters > 100 %
12	11	Base Model 2 + IIV on V1 + OCT effect on CL + Allometric scaling parameters estimated for CL, V1, Q and V2	y	y	-508.9	-7.0	Effect of OCT is still significant in the model with WT covariate + IIV on CL and V1
13	9	Base Model 2 + IIV on V1 + Allometric scaling parameters FIXED for CL, V1, Q and V2	y	n	-477.4	-14.0	The Epsilon and Eta shrinkages for V1 were > 30 % and uncertainty in multiple population model parameters > 100 %
14	13	Base model 2 + IIV on V1 + OCT effect on CL + Allometric scaling parameters FIXED for CL, V1, Q and V2	y	n	-483.7	-6.3	Effect of OCT is still significant in the model with WT covariate + IIV on CL and V1
15	10	Base Model 2 + OCT effect on CL + RACE effect of on CL + Allometric scaling parameters FIXED for CL, V1, Q and V2	y	y	-491.9	-0.49	Effect of Race is not significant after OCT effect is included.
16	12	Base Model 2 + OCT effect on CL + RACE effect on CL + Allometric scaling parameters estimated for CL, V1, Q and V2	y	y	-469.2	-0.54	Effect of Race is not significant after OCT effect is included.

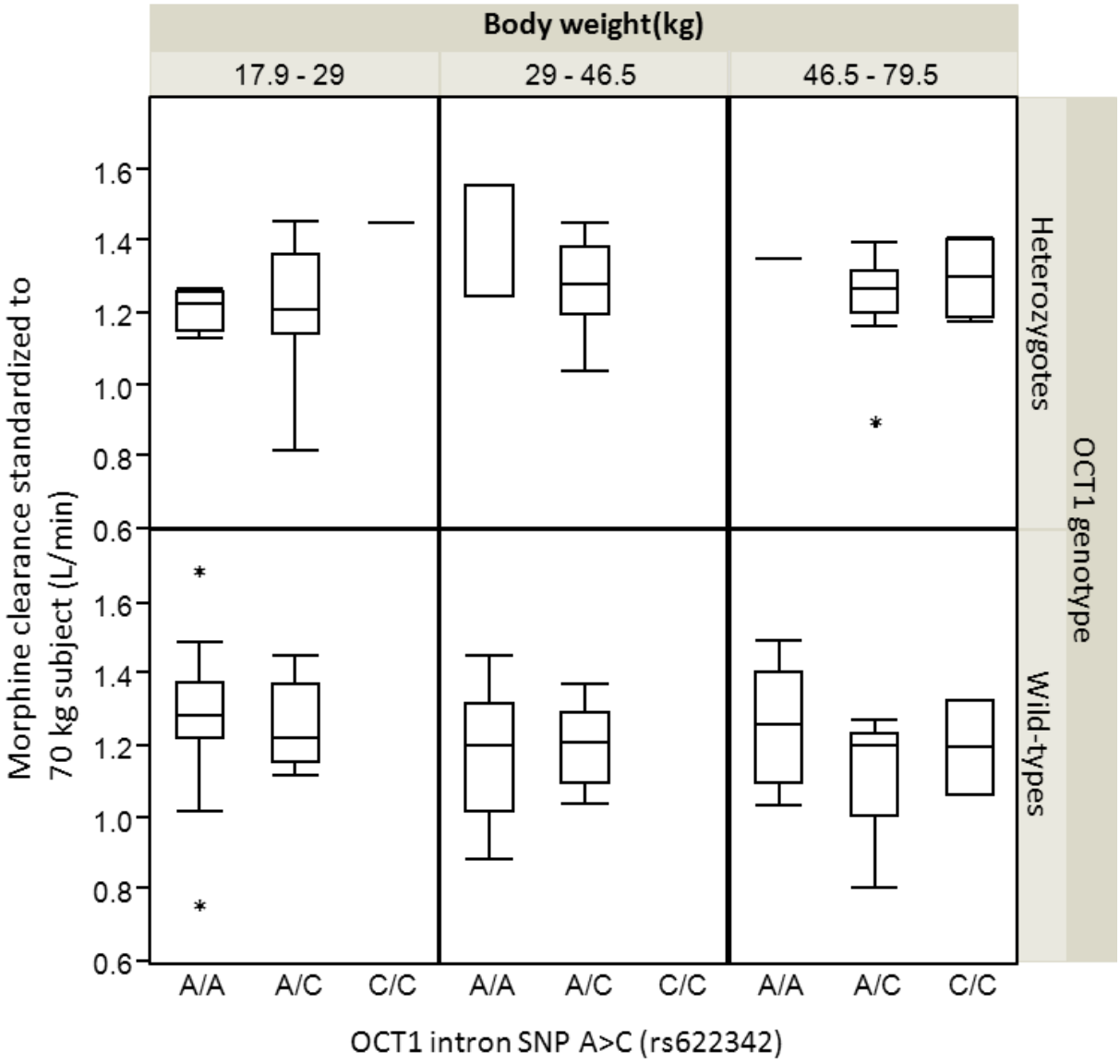
Note: IIV: Inter-individual variability; WT: weight; Est. Succ, Estimate successful; Cov. Step Succ, Covariate step successful; OFV, objective function value; dOFV, delta OFV;



Supplemental Figure 1, Model evaluations for the final pharmacokinetic model.

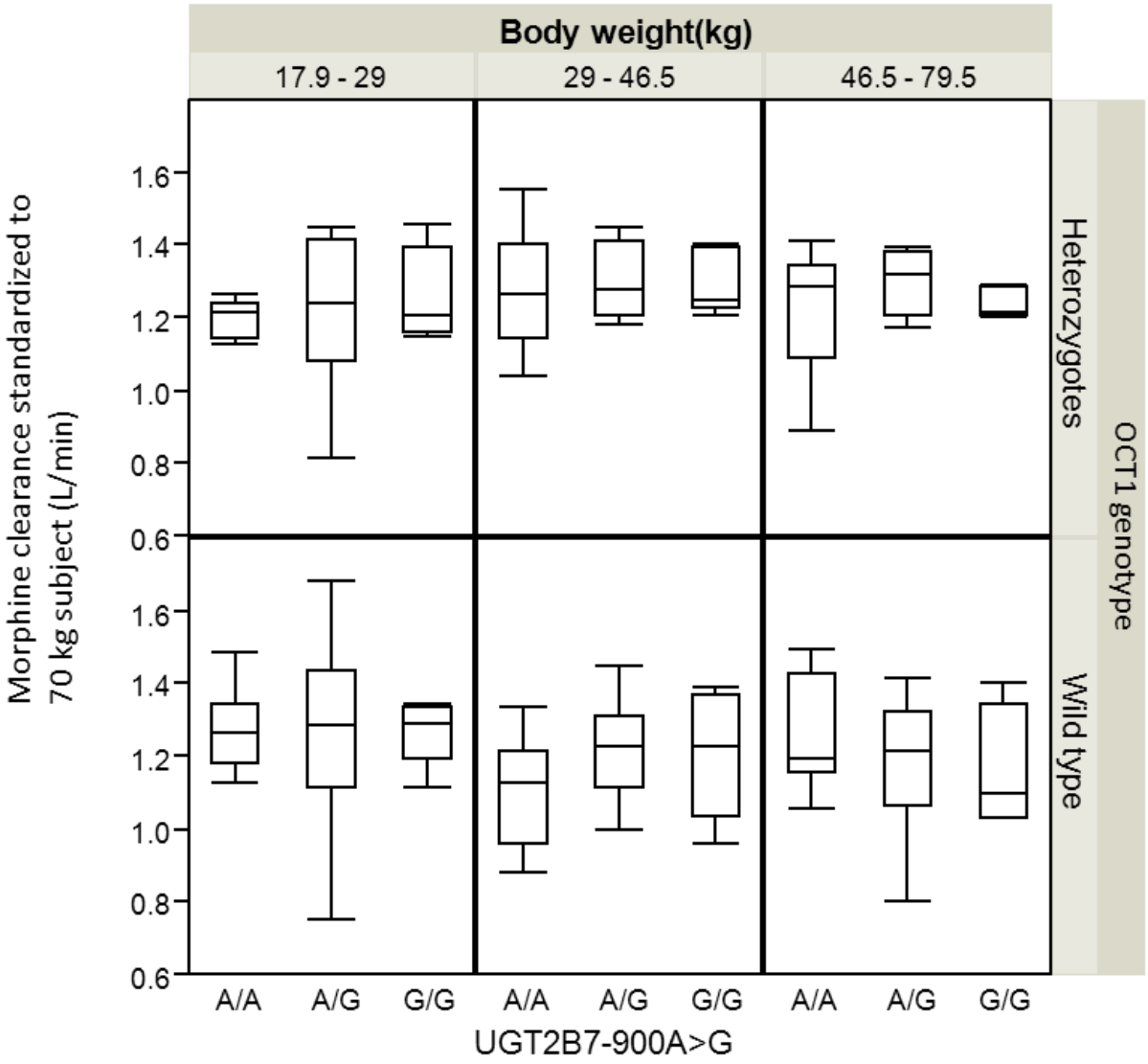
Standard diagnostic plots revealed good model fits without observable trends between the conditional weighted residuals and time, population predictions or covariates.

Examination of the normalized prediction distribution errors (npde) with respect to time, revealed no particular trends. The npde had a mean of -0.003 not significantly different than 0 based on the Wilcoxon signed rank test. Similarly, the variance of the npde's was 0.858, not significantly lower than 1 based on the Fisher variance test. The final model was stable with the bootstrap datasets and successfully fitted the new datasets 1998 times of 2000, and median results comparable to those obtained with the original model.



Supplemental Figure 2, Morphine clearance standardized to a 70kg person versus OCT1 intron SNP.

Subjects in each OCT1 genotype group (heterozygotes and wild-types; as seen on the right y axis) were stratified into three equal sub-groups based on body weight to evaluate potential contribution of OCT1 intron SNP to weight normalized morphine clearance. No meaningful trends were observed within and across these groups suggesting an effect of OCT1 intron SNP on morphine clearance in this study population. Dots (*) represent outliers.



Supplemental Figure 3 Morphine clearance standardized to a 70kg person versus UGT2B7 -900A>G SNP.

Subjects in each OCT1 genotype group (heterozygotes and wild-types; as seen on the right y axis) were stratified into three equal sub-groups based on body weight to evaluate potential contribution of UGT2B7-900A>G to weight normalized morphine clearance. No meaningful trends were observed within and across these groups suggesting an effect of UGT2B7-900A>G SNP on morphine clearance in this study population.