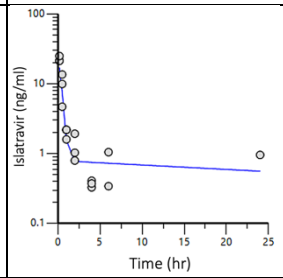
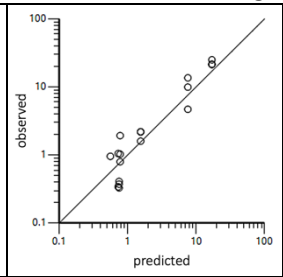
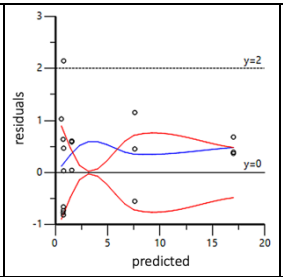
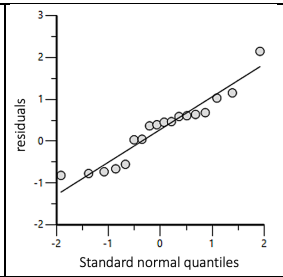
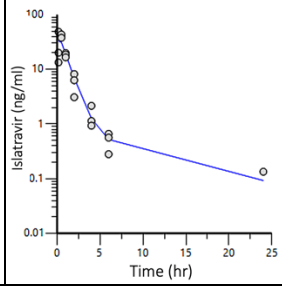
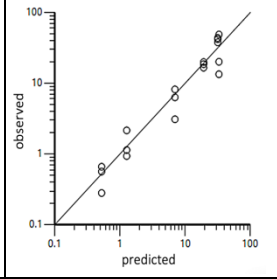
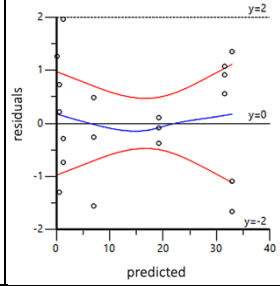
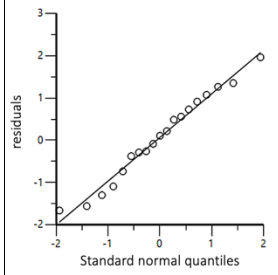
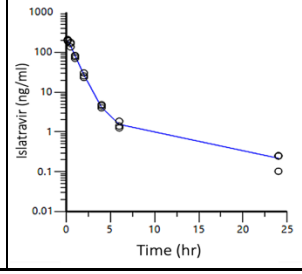
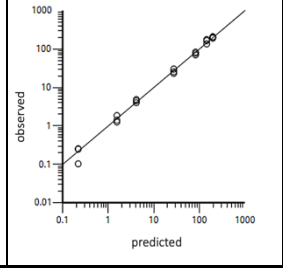
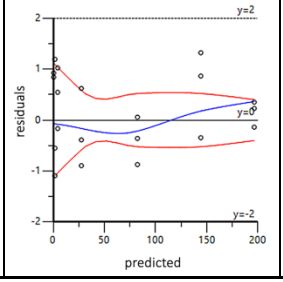
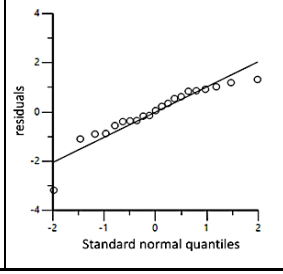
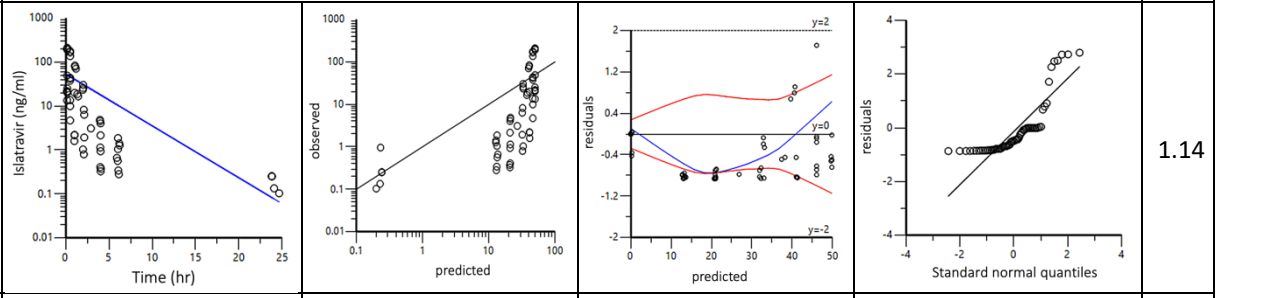
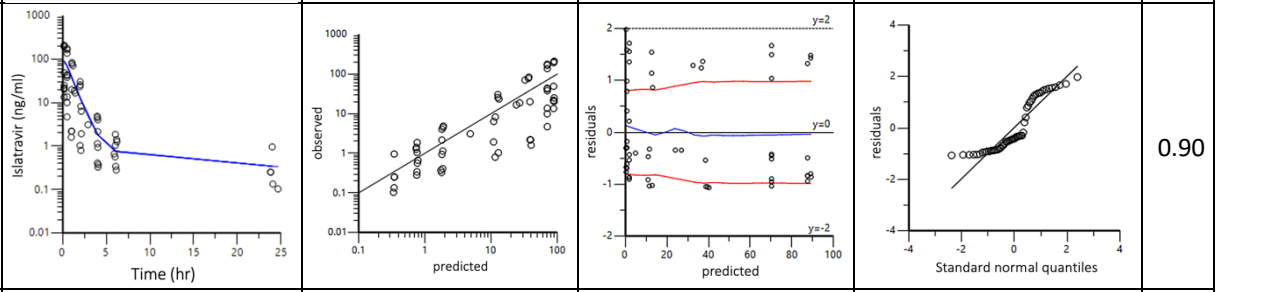
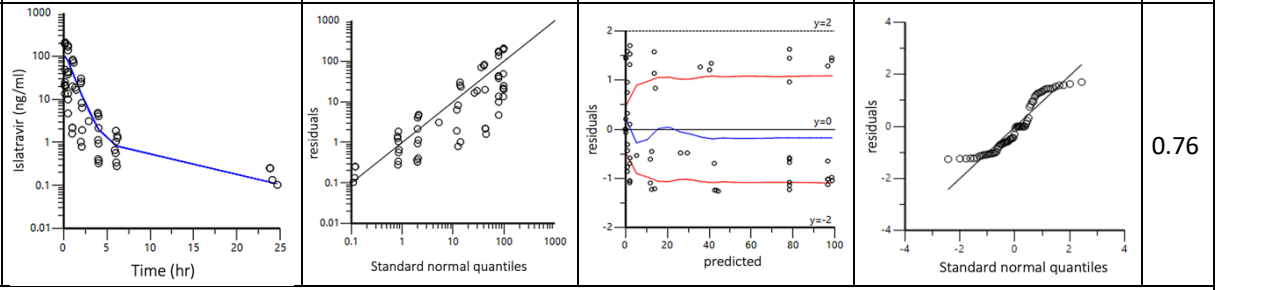
No.		Model	Param	-2LL	AIC	BIC	Diagnostics				RSE
1	**Independent Dose Models**	0.1 mg/kg 2CMT NPD Multi	6	70.7	82.7	88.1					0.69
2		0.2 mg/kg 2CMT NPD Multi	6	81.1	93.8	98.8					0.36
3		1.0 mg/kg 2CMT NPD Multi	6	94.1	106.1	112.4					0.17

No.		Model	Param	-2LL	AIC	BIC	Diagnostics	RSE
4	Simultaneous Dose Model Development	1CMT NPD Multi	4	559.1	567.1	575.9		1.14
5		2CMT NPD Multi [Base Model]	6	414.8	426.4	438.7		0.90
6	Final Model	Base Model no Outlier	6	423.7	435.7	448.9		0.76

Base Model vs. Final Model Theta Parameters

	Final Ka (1/h)	Base Ka (1/h)	Final A (ng/ml)	Base A (ng/ml)	Final alpha (1/h)	Base alpha (1/h)	Final B (ng/ml)	Base B (ng/ml)	Final beta (1/h)	Base beta (1/h)
Estimate	12.23	12.79	141.60	125.66	1.21	1.18	1.39	0.83	0.103	0.037
Std error	2.06	2.12	36.34	35.83	0.06	0.05	0.33	0.30	0.007	0.023
CV%	16.83	16.59	25.7	28.5	4.6	4.1	24.1	36.4	6.6	64.0
2.5% CI	8.11	8.53	68.92	53.76	1.10	1.08	0.72	0.22	0.089	-0.010
97.5% CI	16.34	17.05	214.28	197.57	1.32	1.28	2.06	1.43	0.117	0.083

Circles are observed data; blue lines are predicted curves; red lines are distribution of residuals. CMT- compartment; NPD- naïve pooled; RSE- relative standard error; Ka- absorption rate constant; A- 1st CMT macroconstant; B- 2nd CMT macro-constant; alpha/beta- elimination rate constant; CI- confidence interval.

Table 1: Population pharmacokinetic (PopPK) model development and comparison in Phoenix NLME™.

The population pharmacokinetic (PopPK) analyses were performed using Phoenix NLME modeling software. The model building process was a stepwise approach: independent modeling of islatravir plasma concentration for the three subcutaneous bolus doses (0.1, 0.3 and 1mg/kg), identification of the most appropriate structural base model followed by developing a simultaneous base model of the collapsed dose range. The base structural model was tested for 1, 2 and 3 compartments, describing first-order absorption and linear elimination. The structural model was developed with a fit-for-purpose approach to deconvolution leveraging macro-parameterization to estimate; first-order absorption rate constant (Ka), macro-constants (A and B), elimination rate constants (alpha and beta). A 2-compartment structural models provided a better fit for the collapsed simultaneous model of 0.1, 0.3 and 1.0mg/kg dosing levels. Residual diagnostic plots of the 2-comp Final model show some bias in the fit but do not indicate misspecification as with the 1-comp comparator. A 3 Finally, while AIC increases with addition of a second compartment the-2Loglikelihood decreases (-113). Overall, the fits and criteria indicate an improvement with a 2-compartment structure. Final overall model error decreases from 113% to 76% from a 1 to 2-compartment model when no other factors were changed.

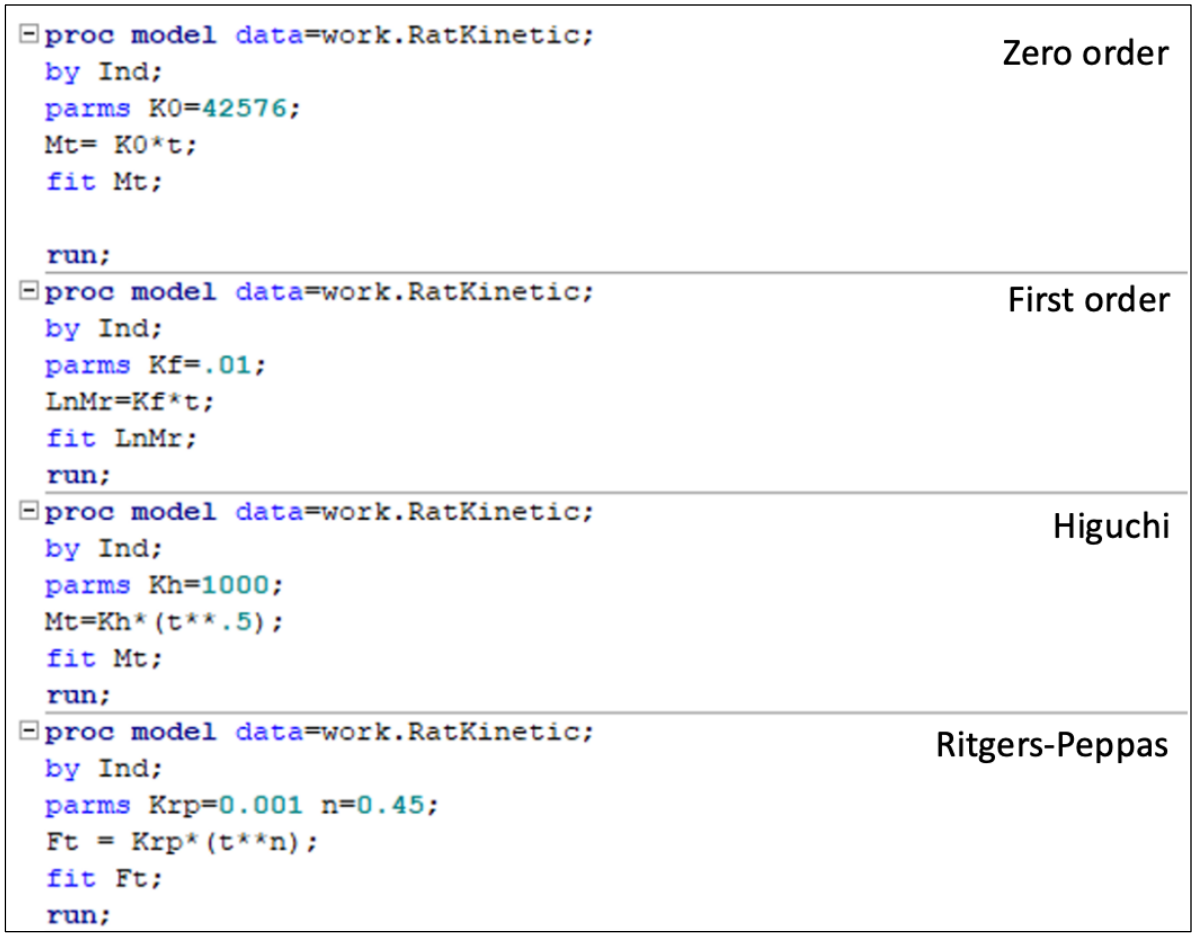


Figure 1: Model code for regression analysis of 4 kinetic models of drug distribution in SAS™ 9.4.

Top down shows each model formula and initial estimate used to fit a regression using the ordinary least squared function. Where *Mt* is the rate constant of each respective model, *Ft* is the ratio of *Mt/Minf* (the mass loaded in the implant), *n* is the power exponent of release, and