MODELING AND SIMULATION OF DRUG X AND ITS METABOLITE IN PLASMA AND URINE

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BACKGROUND

Single ascending dose study of a novel drug administered for the first time in humans.

OBJECTIVE

- Construct a pharmacokinetic (PK) model based on PK plasma and urine concentration data from healthy subjects.
- Characterize the individual and population PK of Drug X and its metabolite after oral administration of the drug using compartmental methods.
- Evaluate the length of time a given drug plasma level was maintained following oral drug administration by simulation.

METHOD

Study Design

- A total of 30 subjects divided into 3 equal groups were used to investigate 6 dose levels of Drug X (3 dose levels over 2 periods). At each dose level, 8 subjects were randomized to receive Drug X and 2 subjects were randomized to receive placebo (no subject received placebo on more than one occasion). For each subject there was a minimum washout period of 3 weeks between dosing.

PK Evaluation

- Blood samples for PK analysis were collected at the following time points: Pre-dose (Hour 0) and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48, 54, 60, and 72 hours post-dose.
- Urine samples for PK analysis were collected over the following intervals: Pre-dose (single void) and at 0-3, 3-6, 6-12, 12-24, 24-48, and 48-72 hours post-dose.

Assay

- Plasma and urine samples were assayed for concentrations of Drug X and its metabolite using a validated LC/MS/MS method.

PK Modeling

- Initial estimates of individual compartmental PK parameters were evaluated using ADAPT II[1]. Concentrations of Drug X and its metabolite in plasma and urine were fitted simultaneously.
- Actual dosing and sampling times were used for the compartmental modeling.
- Model discrimination was performed on data using ADAPT II, by minimizing the Akaike Information Criteria (AIC), the Schwarz Information Criterion (SIC), the residual variability and objective function value (ECV), maximizing the coefficient of determination (r^2) and by comparison of the quality of fit plots (e.g. observed data vs. fitted, weighted residual vs. fitted, weighted residual vs. time).
- Population PK compartmental analysis was performed with IT2S[2] software using the relevant population PK parameters obtained in ADAPT II as prior estimates for the population PK analysis. Hence, the final model was determined with IT2S and optimal estimates of individual PK parameters and their inter-individual variability.
- The variance model of the fitted curves were $(SD_{slope} \cdot Y + SD_{intercept})^2$, where Y was the predicted curve.

RESULTS AND DISCUSSION

Study Design

- The best structural model (Model 14a) for Drug X consisted of 2 compartments with 2 absorption peaks; each associated with a lag time ($Tlag_1$ and $Tlag_2$) and a 1st order absorption rate constant (Ka_1 and Ka_2). All eliminations were non-linear (urine, metabolite and other pathways).
- The model selected for the metabolite was a 1 compartment model. All the eliminations were non-linear (urine and other pathways).
- Model deconstruction was performed with the removal of Vmax and C50 parameters one at a time. The selected model with all 5 Vmax representing the eliminations of Drug X and its metabolite was proven to be the best model.
- The selection of the best structural model was based primarily on the AIC value as well as the quality of fit plots.

Table 1: Model Build-Up Summary for Drug X and its Metabolite

Model No.	Model Description	Median AIC
1	1 Ka, 2 compartment – Drug X; 1 compartment – Metabolite	466.4
2a	2 Ka, 2 compartment – Drug X; 1 compartment – Metabolite	449.1
3a	3 Ka, 2 compartment – Drug X; 1 compartment – Metabolite	504.1
4a	2 Ka, 3 compartment – Drug X; 1 compartment – Metabolite	523.0*
5a	2 Ka, 2 compartment – Drug X; 2 compartment – Metabolite	504.2
6a	2 Ka, 2 compartment and VmaxR – Drug X; 1 compartment – Metabolite	454.3
7a	2 Ka, 2 compartment and VmaxR – Drug X; 1 compartment and mVmaxR – Metabolite	442.3
8a	2 Ka, 2 compartment and VmaxR – Drug X; 1 compartment and mVmaxR and Vmaxnr – Metabolite	443.7
9a	2 Ka, 2 compartment, VmaxR and VmaxF – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	440.0
10a	2 Ka, 2 compartment, VmaxR, VmaxF and CLout – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	428.6**
14a	2 Ka, 2 compartment, VmaxR, VmaxF and VmaxOUT – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	430.4

* Value based on 46 out of 48 converged profiles.
** Lower AIC value relative to Model 14a, however the overall quality of fit was better for Model 14a.

Table 2: Model Deconstruction Summary for Drug X and its Metabolite

Model No.	Model Description	Median AIC
14a	2 Ka, 2 compartment, VmaxR, VmaxF and VmaxOUT – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	430.4
15a	2 Ka, 2 compartment, VmaxR, VmaxF and VmaxOUT – Drug X; 1 compartment and mVmaxR – Metabolite	428.1**
16a	2 Ka, 2 compartment, VmaxR, VmaxF and VmaxOUT – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	477.1
19a	2 Ka, 2 compartment, VmaxF and CLout – Drug X; 1 compartment, Vmaxnr – Metabolite	443.4
20a	2 Ka, 2 compartment, VmaxF and VmaxOUT – Drug X; 1 compartment, Vmaxnr – Metabolite	439.5
21a	2 Ka, 2 compartment and VmaxF – Drug X; 1 compartment, Vmaxnr – Metabolite	447.9
22a	2 Ka, 2 compartment, VmaxF and VmaxOUT – Drug X; 1 compartment, mVmaxR and Vmaxnr – Metabolite	436.8
23a	2 Ka, 2 compartment, VmaxR, VmaxF and VmaxOUT – Drug X; 1 compartment and Vmaxnr – Metabolite	427.1**

** Lower AIC value relative to Model 14a, however the overall quality of fit was better for Model 14a.

Figure 1: PK Structural Model for Drug X and its Metabolite

- Alpha was estimated with the parameter to be between 0 and 1 (Alpha = EXP(P), where P was the ADAPT II or IT2S estimate in the range between 0 to infinity, then Alpha would be forced to be in the range 0-1.
- The molecular weights of the two products were considered in the compartmental model to account for the biotransformation of Drug X to the metabolite.
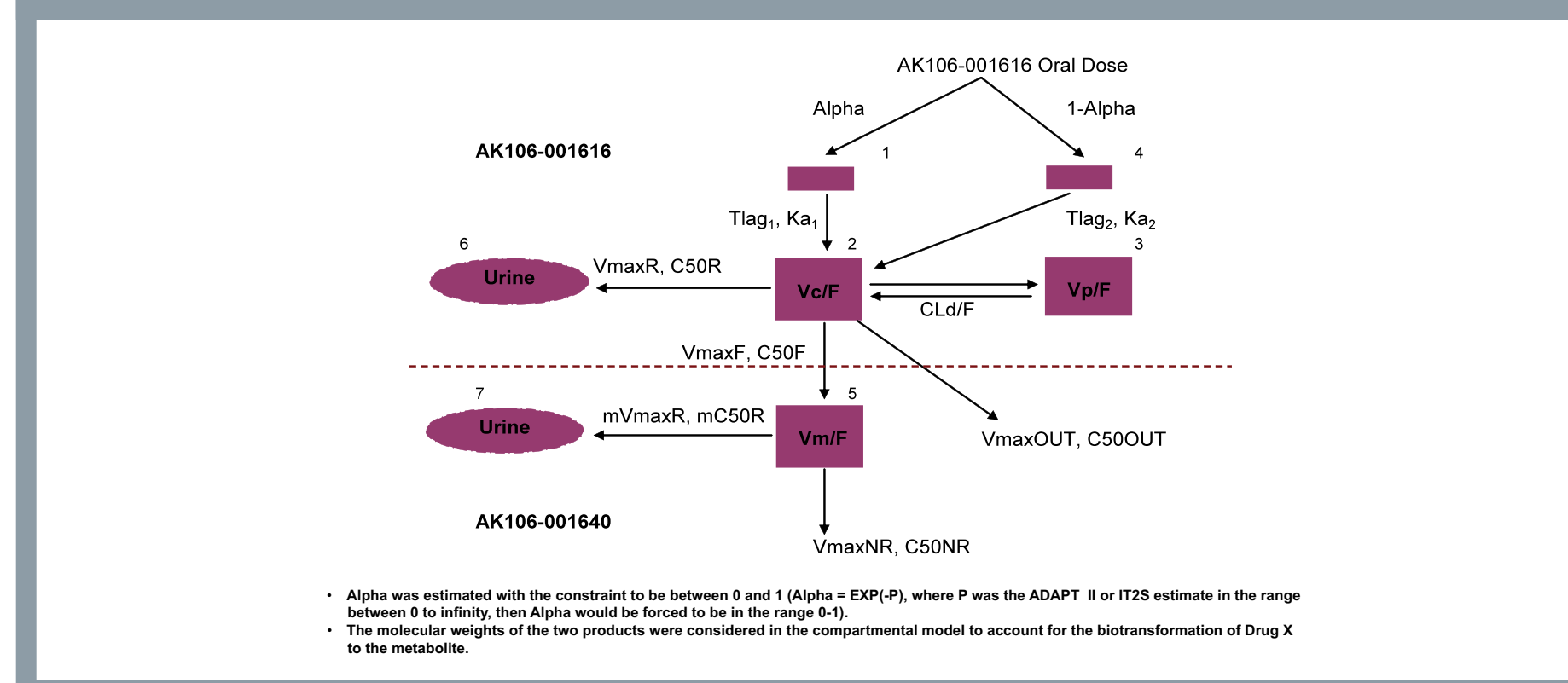

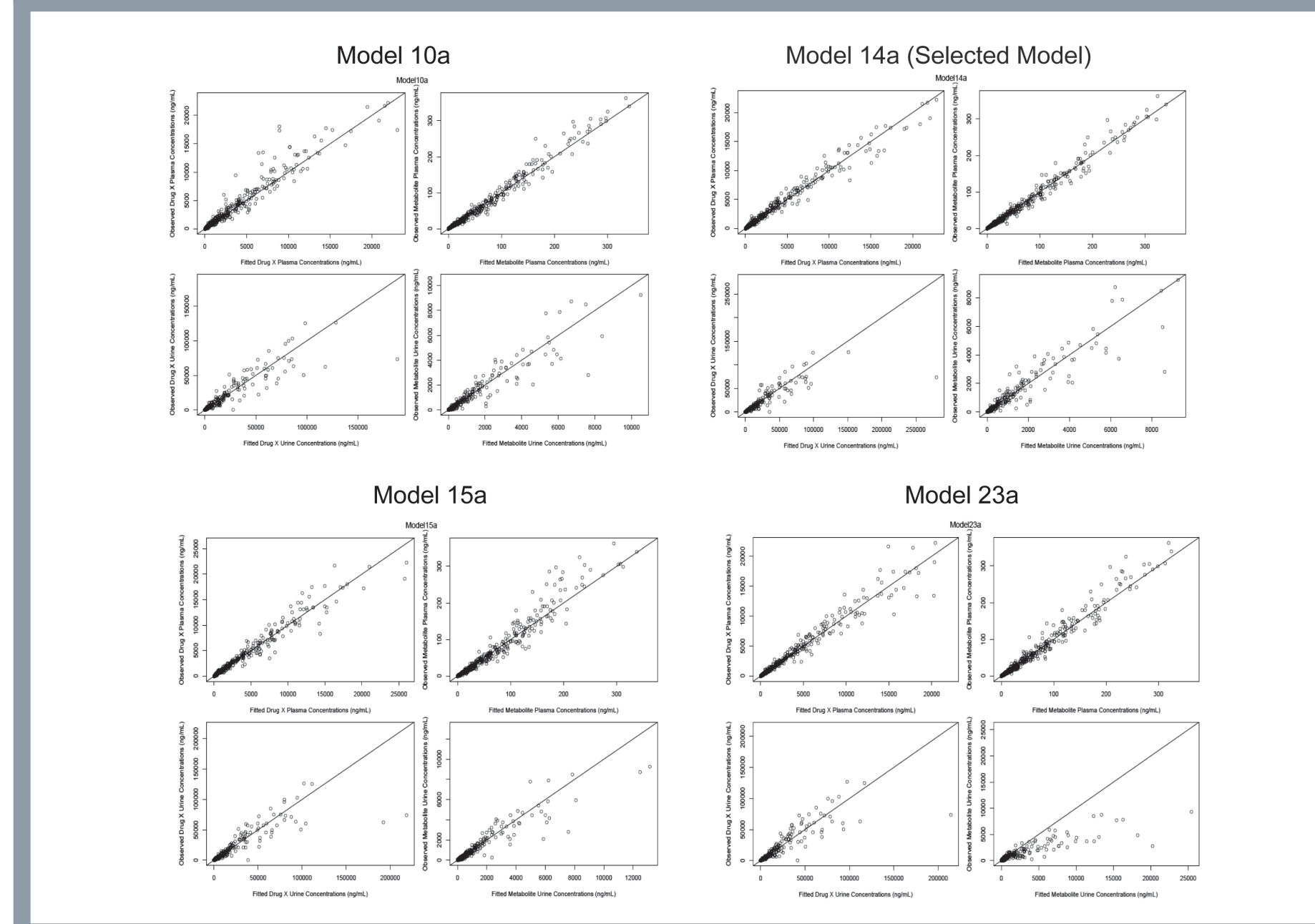Figure 2: Relevant Quality of Fit Plots for Model Discrimination (ADAPT II)

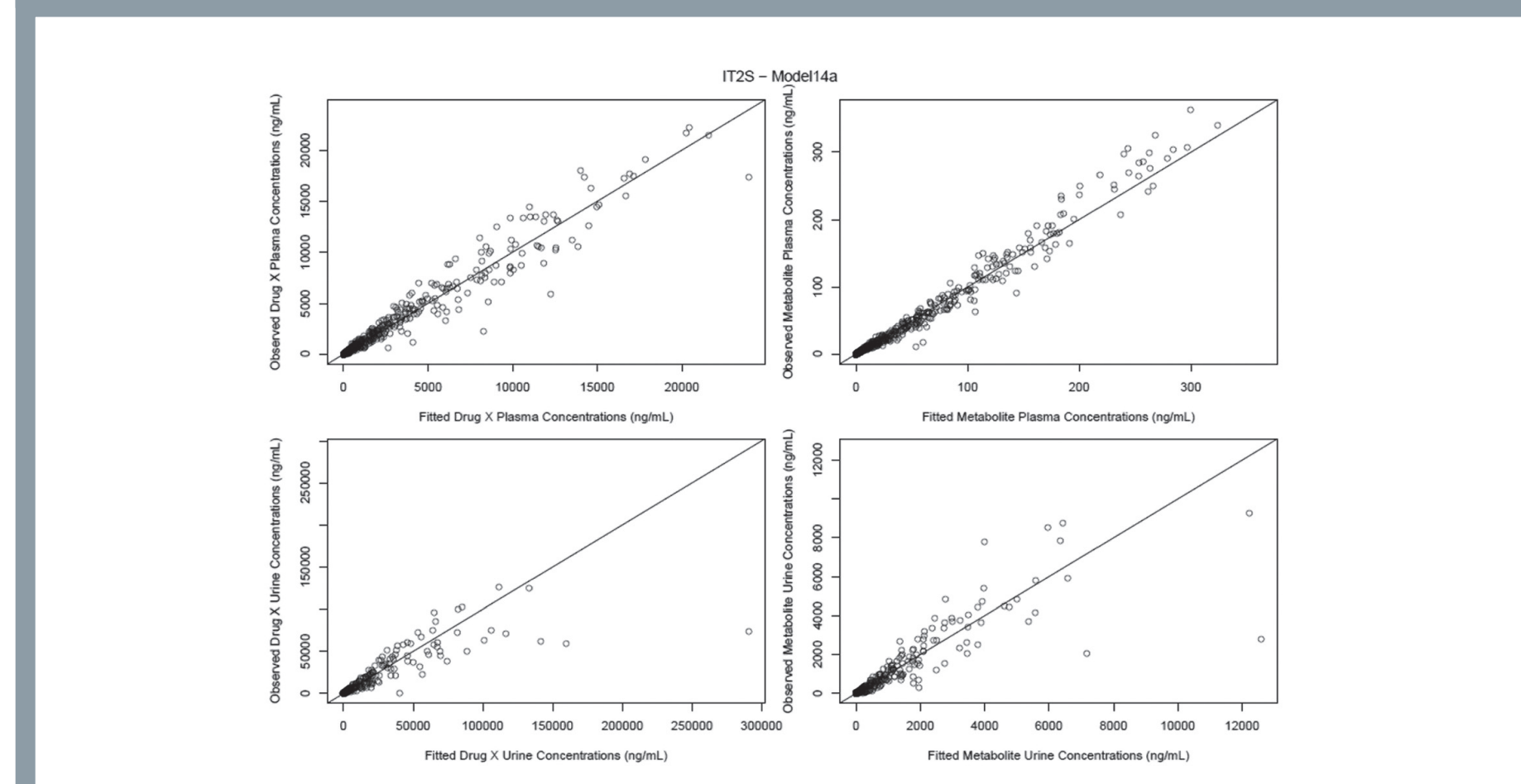Figure 3: Quality of Fit Plots – Observed versus Predicted for Population Analysis (IT2S)

Table 3: SD_{slope}, $SD_{intercept}$ and Residual Variability of the Population PK Model for Drug X and its Metabolite in Plasma and Urine

|	Drug X		Metabolite	
	Plasma	Urine	Plasma	Urine
Predicted $C_{average}$ (ng/mL)	1470	16114	27.5	1013
SD_{slope}	0.283	0.319	0.151	0.37
$SD_{intercept}$	1.66	0.608	0.052	0.449
Residual Variability (%)	28.4	31.9	15.3	37.0

Table 4: Drug X and its Metabolite Population PK Estimates

Parameter (unit)	Mean	Variance
-ln(Alpha)	0.577	0.140
Tlag1(h)	0.447	0.006
Ka1(1/h)	0.453	0.067
Tlag2(h)	2.06	0.585
Ka2(1/h)	1.10	0.423
Vc/F(L)	25.6	103
CLd/F(L/h)	14.3	44.0
Vp/F(L)	124	3281
VmaxR(mcg/h)	7239	6574497
C50R(mcg/L)	4131	2367689
VmaxF(mcg/h)	82769	1097979000
C50F(mcg/L)	7737	10269390
VmaxOUT(mcg/h)	5494	10698750
C50OUT(mcg/L)	151	8990.539
Vm/F(L)	54.9	517
mVmaxR(mcg/h)	235	3318
mC50R(mcg/L)	28.3	108
Vmaxnr(mcg/h)	242141	11012850000
C50nR(mcg/L)	691	89386

The difference in volumes between the central and peripheral compartments of Drug X suggest that it has a higher affinity for protein binding in tissues in the peripheral compartment than for the tissues in the central compartment.

Table 5: Clearance and Half-life versus Concentrations of Drug X and its Metabolite Based on Individual Estimates

Parameter	Arithmetic Mean
CLr(C=0) (L/h)	1.82
CLr(C=24000) (L/h)	0.254
CLf/F(C=0) (L/h)	13.0
CLf/F(C=24000) (L/h)	2.66
CLout(C=0) (L/h)	55.3
CLout(C=24000) (L/h)	0.261
CL/F(C=0) (L/h)	70.1
CL/F(C=24000) (L/h)	3.17
(CLf/F)/(CL/F)*100 (C=0) (%)	22.8
(CLf/F)/(CL/F)*100 (C=24000) (%)	82.7
HL-λz (C=0) (h)	7.95
HL-λz (C=24000) (h)	39.4
CLmr(C=0) (L/h)	9.01
CLmr(C=360) (L/h)	0.602
CLnr (C=0) (L/h)	434
CLnr (C=360) (L/h)	253
CLm/F (C= 0) (L/h)	443
CLm/F (C= 360) (L/h)	253
HL-K10m (C=0)	0.115
HL-K10m (C=360)	0.177

Figure 4: Total Clearance of Drug X and its Metabolite in Plasma versus Concentration
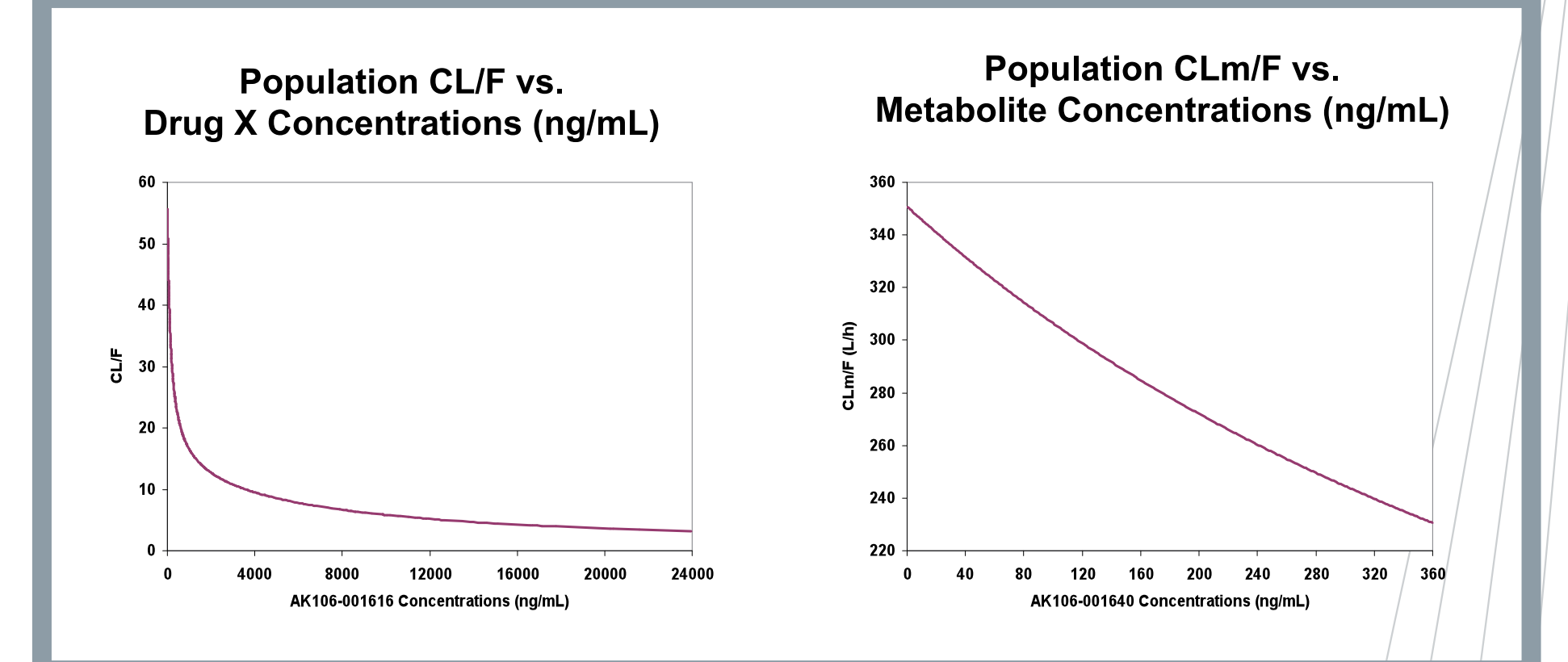
- Total clearance of Drug X (CL/F) appears to decrease with increasing concentrations. Table 5 presents estimates for the clearance of the drug with no concentration (C=0) and at high concentrations observed in the study for the both the parent and metabolite in plasma. Clearances were calculated with the formula CL = Vmax/(C50 + Concentration).
- Clearance of Drug X appears to be predominately non-renal in nature. Assuming that the absolute bioavailability (F) is equal to one, approximately 20% [(CLf/F)/(CL/F)*100] of Drug X was transformed into the metabolite when there was no drug concentration (C=0 ng/mL), and increased up to approximately 82% when the concentrations were high (C=24000 ng/mL). However, at the $C_{average}$ concentration (1470 ng/mL) the percentage of Drug X transformed into the metabolite was approximately 63% with approximately 9% being excreted renally.
- The inability of the subjects to clear the drug and metabolite can also be seen in the increase in elimination half-life with increasing dose. This increase in half-life was more prominent with Drug X than for the metabolite. At a concentration of zero the half-life of the parent was approximately 8 hours but increased to almost 40 hours when the plasma concentrations reached 24000 ng/mL (calculations are theoretical based on a 2 compartment model with linear elimination).

SIMULATION

- A simulation was performed in order to assess the length of time per day following the administration of a dose of 100 mg/day BID would maintain minimal plasma concentration of 100 ng/mL. One thousand profiles were simulated with ADAPT II. Values used for the simulation were taken from the population analysis performed with IT2S. The simulation was performed so that every 0.1 hour a concentration estimate would be obtained. The lag times were not simulated; they were fixed to the population value.
- Calculations were performed on estimates obtained on Day 9. Approximately 78.8% of the simulated concentrations were greater or equal to 100 ng/mL accounting for about 18.9 hours out of a 24-hour day.

Figure 5: 1000 Profiles Simulated with 100 mg BID of Drug X (Day 9)
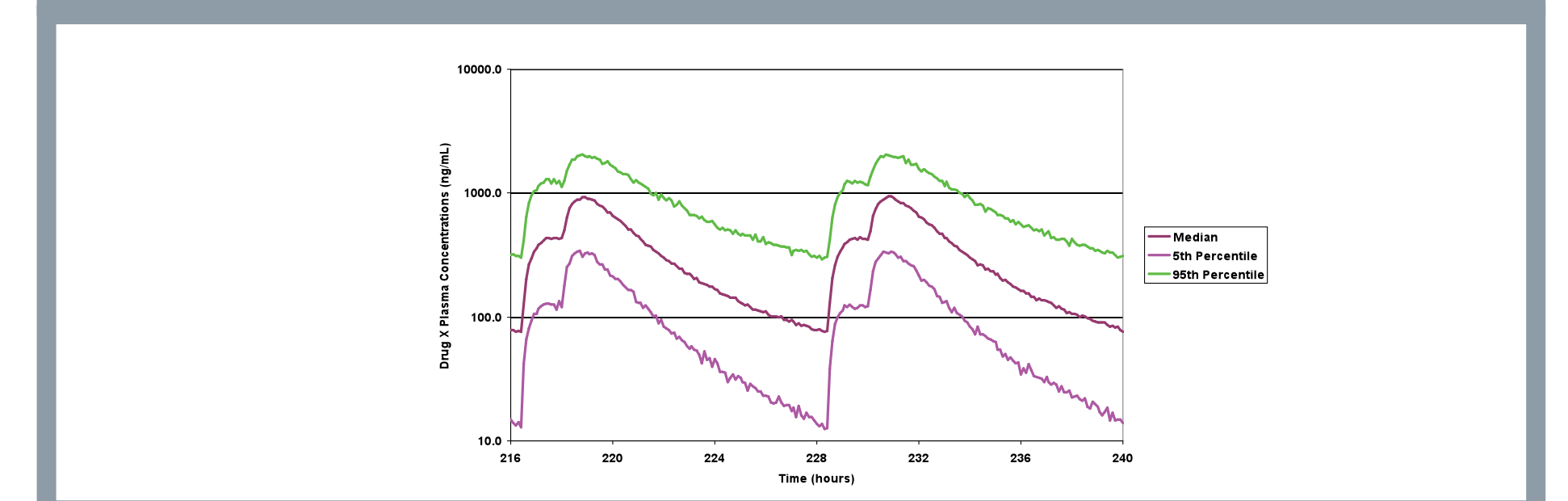
CONCLUSION

- Drug X followed a 2 compartment PK model with 2 first order absorptions, 2 lag times and all the eliminations (urine, metabolite and other pathways) were non-linear.
- The metabolite followed a 1 compartment PK model and all the eliminations (urine and other pathways) were non-linear.
- The elimination half-life increased with increasing dose. This increase in half-life was more prominent with Drug X than for the metabolite.
- Simulated concentrations were greater or equal to 100 ng/mL accounting for about 18.9 hours out of a 24-hour day following a 100 mg BID dose of Drug X. Simulated results were obtained following multiple doses.

REFERENCES

1. D'Argenio DZ, Schumitzky A. ADAPT-II Users Manual. Biomedical Simulations Resource, University of Southern California, Los Angeles, 1997.
2. Collins DG, Forrest A. IT2S User's Guide. State University of New York at Buffalo, Buffalo: 1995.

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