

Development of a population PKPD model
using NONMEM® - Case Study III

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The [first step](#) is to build a population PK model. A one compartment zero order input model was used based on preliminary data analysis. Individual PK parameter estimates are obtained.

- The [second step](#) is to develop a PD model. There are primarily two ways to perform PKPD modeling, simultaneous and sequential PKPD modeling approach. In simultaneous modeling, both PK and PD modeling is done simultaneously. In the sequential approach, PK model is developed and parameter estimates obtained in the first step. In the second step, Individual parameter estimates from the PK analysis is used to drive the PD modeling. Sequential PKPD modeling approach is used in this case study. Based on the drug's mechanism of action, an inhibitory indirect response model was chosen.

[Creating data file for PK analysis](#)

This is similar to case-study 1, except that a RATE column specifies the infusion rate. The comma delimited data file consists of data obtained from 20 individuals who were infused 100mg over 6 hours. A sample NONMEM data file for this study looks the following:

C	Intravenous infusion-One compartment-Single dose Study					
C	No.of Subjects=20, AMT=Dose=100 mg for 6hr at 16.7mg/hr					
C	Time in hrs, CONC=Plasma Concentration in ng/ml, Clearance=L/hr, Volume=L					
CID	TIME	CONC	AMT	RATE	MDV	
1	0	0	100	16.7	1	
1	0.5	94.324	0	0	0	
1	1	202.81	0	0	0	
1	3	428.36	0	0	0	
1	5	678.33	0	0	0	
1	6	590.98	0	0	0	
1	8	450.33	0	0	0	
1	12	233.45	0	0	0	
1	15	156.33	0	0	0	
1	18	86.048	0	0	0	

Explanation of the data file columns

Column name	Description	Required or optional
ID	subject identification number. It is written as CID, where C = default NONMEM recognized symbol for ignoring any data from data file.	Required item
TIME	Blood sampling time. Should be chronologically arranged.	Required
CONC = DV	Plasma concentration in this case, could be any dependant variable i.e., biomarker concentration or tissue concentration, plasma concentration	Required
AMT	Dose administered at dosing time or zero for observation records	Required
RATE	Infusion rate, given the infusion rate NONMEM calculates the duration of infusion.	Required for a zero – order input
MDV	Missing dependant variable, takes value as 1, when observation is missing, otherwise zero.	Optional

The data file created is stored as .csv file in any working directory for the project or in the same folder as the control stream.

[Click here for link to the data file](#)

[Control stream for structural PK model](#)

The control stream (with explanations for each line) for the structural model, which is a one-compartment intravenous infusion model based on preliminary data analysis, is given below. The initial estimates for PK parameters were obtained from preliminary data analysis and non-compartmental analysis. Analysis in NONMEM® was performed by using a first order (FO) estimation method. Results from other estimation methods namely, first order conditional estimation (FOCE) and FOCE with interaction are also provided in the end for comparison.

[Click here for the control stream.](#) (Download the control stream, copy the contents in Notepad and save it in the working directory with a .ctl extension)

[Performing the NONMEM run](#)

- NONMEM execution was done using Wings for NONMEM (WFN) developed by Dr.Nick Holford, available at <http://wfn.sourceforge.net/> WFN is a set of DOS batch command files and awk scripts. The various features of WFN are described at the above mentioned website.
- Click the command prompt icon configured for WFN (This could be done when installing WFN) and open the working directory (The path could also be stored).
 - ¾ When using WFN, Type nmgo XXXX (The name of the control stream, No need to type the .ctl extension) to perform the NONMEM run.

[Viewing and interpreting the output file](#)

- When each control stream is run, an output folder is created in the same working directory from where the NONMEM run was performed.

- In the output folder, there is a summary file with a **.smr** extension, a detailed output file with **.lst** extension and the table output in a **.fit** extension.

For this case study, the output from the **.lst** file is explained and interpreted. Diagnostic plots are created using the table output with a **.fit** extension using S-Plus®

MINIMUM VALUE OF OBJECTIVE FUNCTION

1683.238 → NONMEM calculates the objective function value by extended least squares method and is equivalent to -2 times the maximum log of the likelihood of the data ($-2LL$).

FINAL PARAMETER ESTIMATE OF PK MODEL

THETA - VECTOR OF FIXED EFFECTS PARAMETERS

TH 1	TH 2
2.28E+01	7.89E+01

↙ ↘

CL_{pop} = 22.8L/hr **V_{pop} = 79L**

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

	ETA1	ETA2
ETA1		
+	6.51E-02	→ BSV on CL == 25% (sqrt(0.06*100))
ETA2		
+	0.00E+00	1.02E-01 → BSV on V == 32%

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

	EPS1	EPS2	
EPS1			
+	2.18E-02		→ WSV (Proportional error): == 14%
EPS2			
+	0.00E+00	2.82E+01	→ WSV (Additive error): == 5.3ng/ml

STANDARD ERROR OF ESTIMATES

THETA:se%	= 5.7	6.6	→	Precision of PK parameters
OMEGA:se%	= 25.0	50.5	→	Precision of BSV parameters
SIGMA:se%	= 21.1	30.6	→	Precision of WSV parameters
	↙	↘		
	Proportional error	Additive error		

[Diagnostic plots for structural PK model and interpretation](#)

The first plot to look at would be a plot of concentration (observed (DV), individual predicted (IPRED) and population predicted (PRED)) versus time for all the individuals. A representative plot of few individuals is provided below. This plot would give an overall trend of fitted concentrations.

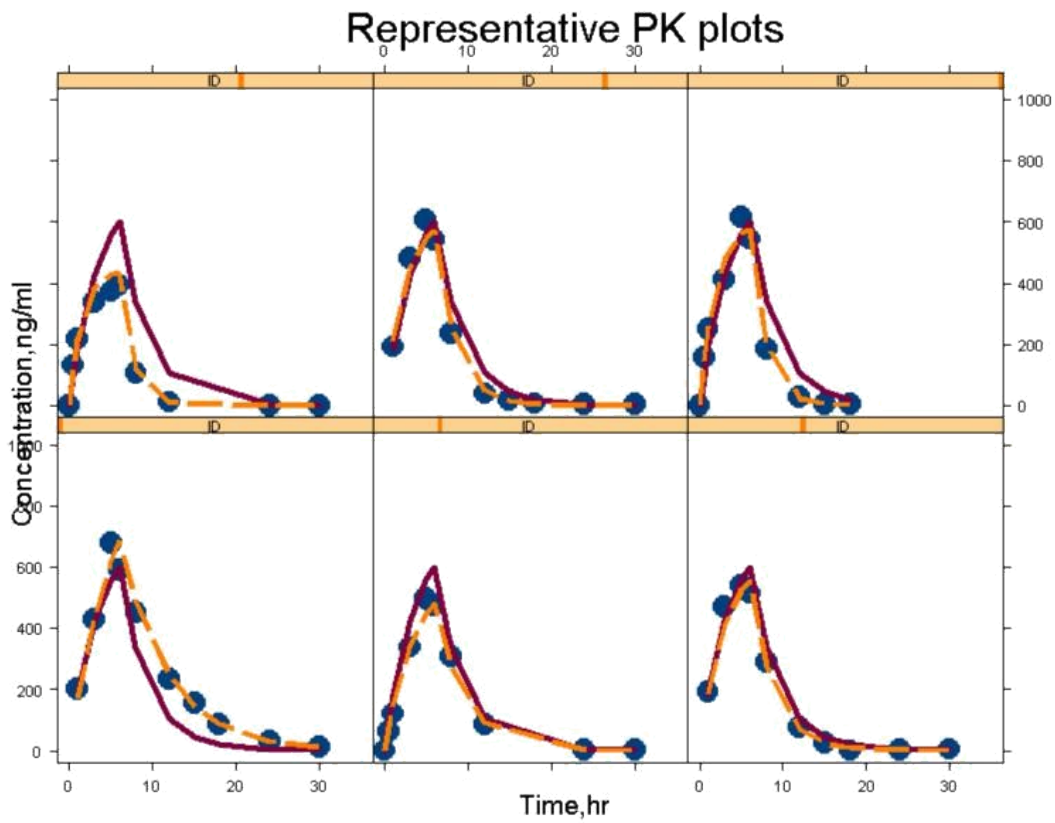


Figure 1: Plot of observed (•), individual predicted (-----) and population predicted (-----) drug concentration versus time.

The second set of diagnostic plots would be the following.

- DV vs IPRED and DV vs PRED: These graphs could be looked for any bias in the predictions. Ideally the points should be uniformly distributed along the line of identity. The graph below shows uniformly distributed points on either side of line of identity.

Observed vs predicted concentrations - PK

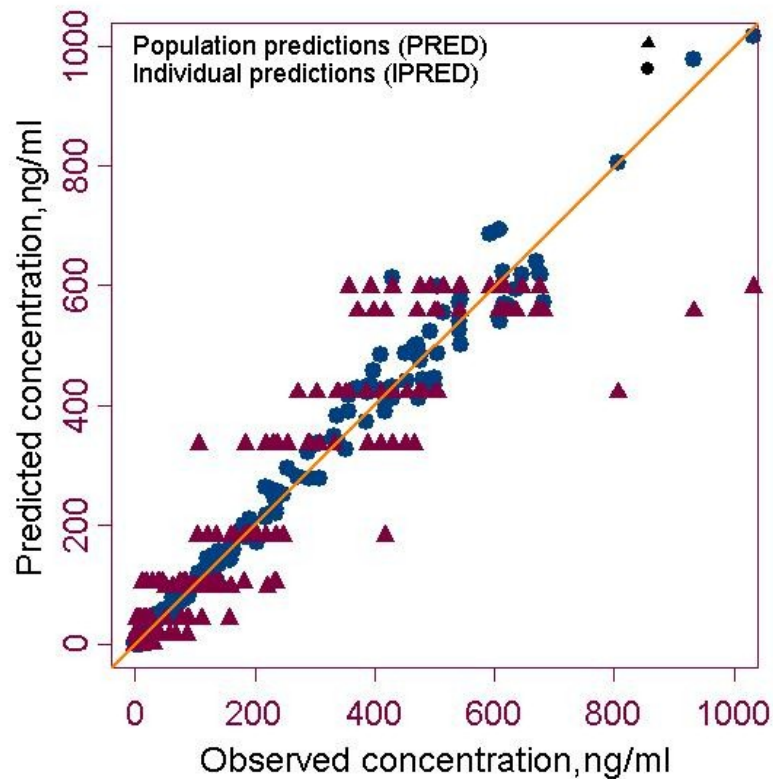


Figure 2A: Goodness of fit plots (• - Observed vs individual predicted concentration, ▲ - Observed vs population predicted)

- RES vs PRED and WRES vs PRED: Residual plots are looked for any unaccounted heterogeneity in the data.
- Note: Though residual plots are some of the goodness of fits plot explored, the utility of these residual plots is not well documented.

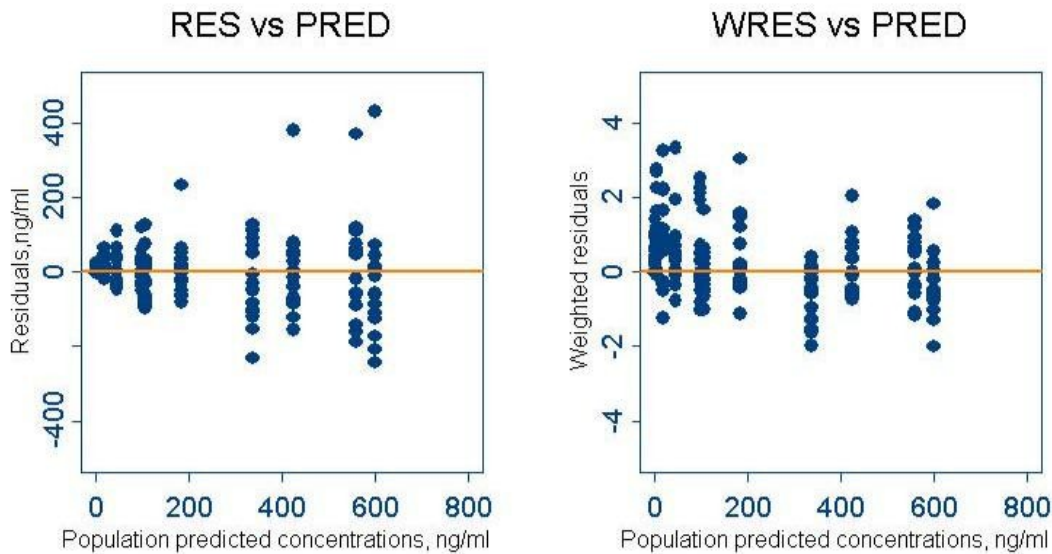


Figure 2B: Goodness of fit plots (Residuals & Weighted residuals vs Population predicted concentration)

[Developing PD model](#)

Now that the PK model is well defined, bayesian individual parameter estimates are used for PK-PD modeling.

[Creating data file for PKPD model](#)

The following example shows the data file for sequential PKPD modeling approach used in this case-study (III). The explanation of the data file is provided in the initial rows. The pd data and the information for PK namely CL and V from the PK fit file is merged using S-Plus®. The codes are provided below:

```

> cs3pd <- read.table("c:\\..\\cs3_ivinfpd_spl.us.fit", header = TRUE, skip = 1)
  #import the pd data
> cs3pk <- read.table("c:\\..\\cs3_ivinfest.fit", header = TRUE, skip = 1)
  #import the pk fits output table
> cs3ivinfpkpd <- cbind(cs3pd, rep((cs3pk[(cs3pk$AMT == 100), ])$CL, each = 14),
rep((cs3pk[(cs3pk$AMT == 100), ])$V, each = 14))
  #Combine the pd data along with CL and V from pk output table
  #Number of rows for each ID in the pd dataset is different from pk dataset, because of
pd initialization, therefore extract each CL and V from pk dataset and repeat them to match the
no of rows for each ID.
> names(cs3ivinfpkpd) = c("CID", "TIME", "HIST", "AMT", "CMT", "RATE", "MDV", "CLI", "VI")
> exportData(cs3ivinfpkpd, file = C:\\..\\cs3_ivinfpkpdest.csv", type = "ASCII", quote = F)
  #Export data to working folder for NONMEM. Note: the file name is different for
illustration purposes.

```

CID	TIME	HIST	AMT	CMT	RATE	MDV	CLI	VI
C	SEQUENTIQL PK-PD MODELING							
C	Single dose intravenous infusion of drug, PD biomarker is Blood histamine concentration (ng/ml)							
C	CMT = 1=Plasma, CMT=2=Effect, CLI & VI are individual parameter estimates							
C	PK is predicted from parameter estimates and drives PD modeling							
1	0	0	100	1	16.7	1	15.585	90.812
1	0	0	1	2	0	1	15.585	90.812
1	0	13.008	0	2	0	0	15.585	90.812
1	0.5	13.808	0	2	0	0	15.585	90.812
1	1	8.6859	0	2	0	0	15.585	90.812
1	3	6.2601	0	2	0	0	15.585	90.812
1	5	4.0602	0	2	0	0	15.585	90.812
1	6	4.4985	0	2	0	0	15.585	90.812
1	8	3.2736	0	2	0	0	15.585	90.812
1	12	2.6026	0	2	0	0	15.585	90.812
1	15	2.3422	0	2	0	0	15.585	90.812
1	18	3.8008	0	2	0	0	15.585	90.812
1	24	7.1397	0	2	0	0	15.585	90.812
1	30	8.9367	0	2	0	0	15.585	90.812
2	0	0	100	1	16.7	1	19.008	91.378
2	0	0	1	2	0	1	19.008	91.378
2	0	19.323	0	2	0	0	19.008	91.378

Note: To initialize PD compartment an extra row having AMT = 1 at time = 0 for the effect compartment needs to be specified.

[Click here](#) for the PD data file used for the study

[Control stream for PKPD model](#)

A plot of effect versus concentration showed anti-clockwise hysteresis, indicating a delayed effect. T_{Rmax} (Time for maximum response) occurs much later than t_{max} . Based on drug's mechanism of action, an inhibitory indirect response model is chosen. To learn how to obtain initial estimates for kin , $kout$ and $IC50$, please refer Dayneka et al, 1993:

[Click here for control stream for PKPD model](#)

[PKPD model output and interpretation](#)

Another way to read the output is from **.smr** file in the output folder.

PARAMETER ESTIMATES FOR PK-PD MODEL

THETA:	kin	kout	IC50
ETA:	BSV kin	BSV kout	BSV IC50
ERR:	CCV	ADD	
CS3_IVINFPDEST.lst	686.564	eval=162 sig=+3.4 sub=20 obs=240	
THETA	= 7.59	0.331	6.82
ETASD	= 0.459347	0.30315	0.367423
	↙	↘	↘
	BSV_{kin} = 46%	BSV_{kout} = 30%	BSV_{IC50} = 37%
ERRSD	= 0.110454	0.857904	
	↙	↘	
	Proportional error = 11%	Additive error = 0.86ng/ml	

STANDARD ERROR OF ESTIMATES

THETA:se%	= 11.0	8.9	13.0
OMEGA:se%	= 33.9	27.2	37.8
SIGMA:se%	= 21.1	37.2	

[Diagnostic plots of PKPD model](#)

Representative individual fits of blood histamine concentrations versus time by the inhibitory indirect response model is shown below.

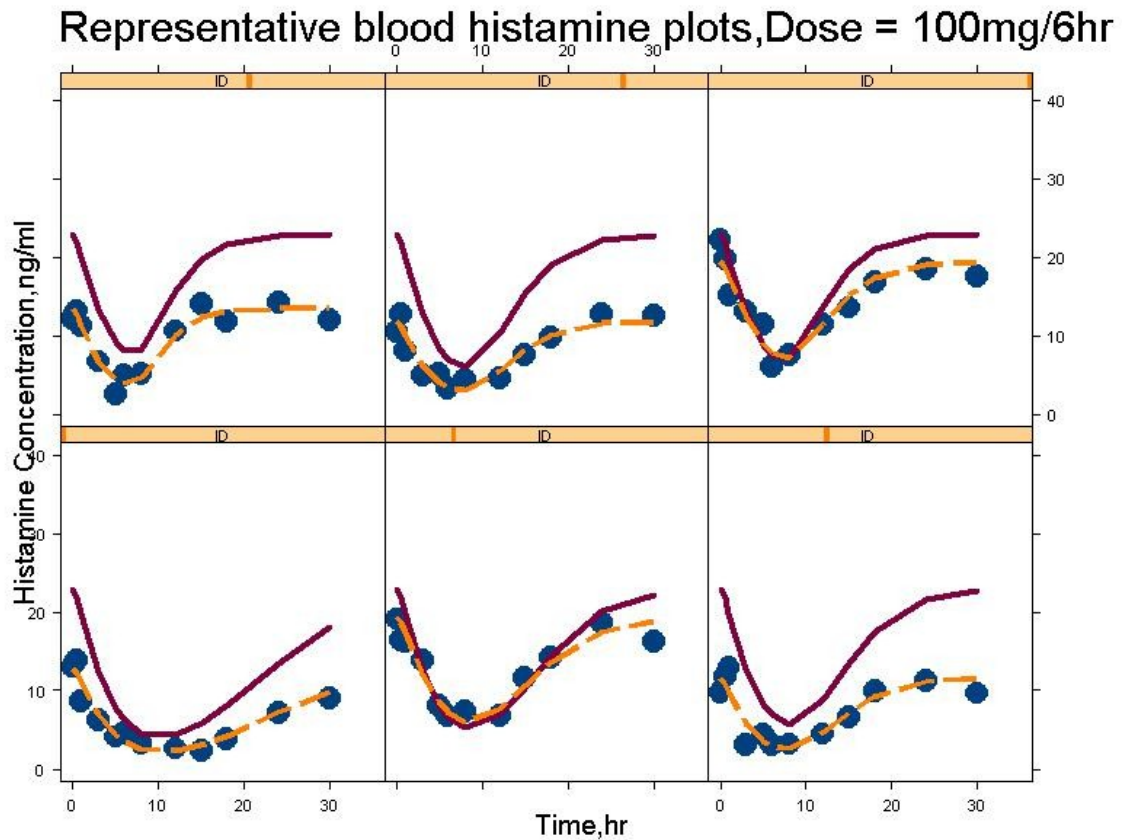


Figure 3: Plot of observed (•), individual predicted (-----) and population predicted (____) histamine concentration versus time.

Another goodness of fit plot is that of observed versus the predicted (population and individual) concentration as shown below for the PKPD model.

Observed vs predicted concentrations - PD

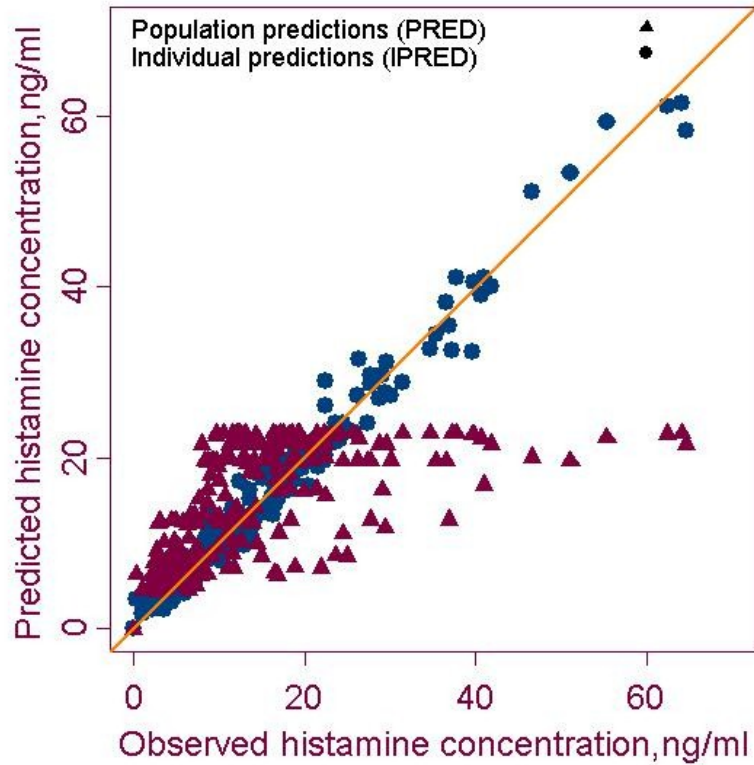


Figure 4: Goodness of fit plots (• - Observed vs individual predicted concentration, ▲ - Observed vs population predicted)

[Compilation of results](#)

The results obtained could be compiled and documented according to the user's documentation procedure. Following is a way of compiling the results. Below, are results from FO approximation.

Model	Population estimate (%SE)	Between subject variability (%SE)
PK model iv infusion 1 cmt $CL = CL_{pop} \cdot \eta_{CL}$ $V = V_{pop} \cdot \eta_V$		
CL (L/hr)	22.8 (5.7)	25 % (25)
V (L)	79 (6.6)	32 % (51)
Residual variability		
Proportional error	15 (21)	
Additive error	5.3 ng/ml (30)	
PKPD model Inhibitory indirect response model $dR/dt = k_{in} \cdot (1 - (C/IC_{50} + C)) - k_{out} \cdot R$		
k_{in} (ng/ml/hr)	7.6 (11)	46 % (34)
k_{out} (hr⁻¹)	0.33 (9)	30% (27)
IC₅₀ (ng/ml)	6.8 (13)	37% (38)
Residual variability		
Proportional error	11% (21)	
Additive error	0.85 ng/ml (37)	

Below, are results from FOCE approximation.

Model	Population estimate (%SE)	Between subject variability (%SE)
PK model		
iv infusion 1 cmt		
$CL = CL_{pop} \cdot \eta_{CL}$		
$V = V_{pop} \cdot \eta_V$		
CL (L/hr)	23.7 (6.1)	26.7 % (30)
V (L)	77.2 (7.6)	31.6 % (35)
Residual variability		
Proportional error	10.9 (18.)	
Additive error	3.4 ng/ml(34)	
PKPD model		
Inhibitory indirect response model		
$dR/dt = k_{in} \cdot (1 - (C/IC_{50} + C)) - k_{out} \cdot R$		
kin (ng/ml/hr)	7.4 (11)	48.3 % (32)
kout (hr⁻¹)	0.37 (7.7)	27.8% (30)
IC₅₀ (ng/ml)	6.7 (9.1)	32% (29)
Residual variability		
Proportional error	11% (21)	
Additive error	0.94 ng/ml (35)	

Below, are results from FOCE with interaction approximation method.

Model	Population estimate (%SE)	Between subject variability (%SE)
PK model		
iv infusion 1 cmt		
$CL = CL_{pop} \cdot \eta_{CL}$		
$V = V_{pop} \cdot \eta_V$		
CL (L/hr)	24.4 (6.1)	26.8 % (29)
V (L)	74.2 (7.0)	30.6 % (35.4)
Residual variability		
Proportional error	10.1 (17.0)	
Additive error	3.3 ng/ml (26)	
PKPD model		
Inhibitory indirect response model		
$dR/dt = k_{in} \cdot (1 - (C/IC_{50} + C)) - k_{out} \cdot R$		
kin (ng/ml/hr)	7.5(10.8)	42 %(32.1)
kout (hr⁻¹)	0.38 (7.2)	27.5% (34.3)
IC₅₀ (ng/ml)	6.7 (8.8)	31.4% (40.4)
Residual variability		
Proportional error	9.6% (31)	
Additive error	1.11 ng/ml (24)	