

Adapting a Target-mediated Drug Disposition (TMDD) Model to Account for Delayed t_{max} Following IV Infusion of a Monoclonal Antibody

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Answers That Matter.

ABSTRACT

Objective: The aim of the analysis was to build a semi-mechanistic model to describe the PK of a monoclonal antibody administered by IV infusion.

Methods: A population pharmacokinetic (PK) analysis was conducted using NONMEM version 7.2 to describe the IV-infusion data. Estimation methods included first order conditional estimation with interaction (FOCEI), Monte Carlo importance sampling expectation maximization (IMP), and IMP assisted by mode a posteriori estimation (IMPMPAP). The final model was selected based upon change in objective function value (OFV), precision estimates, diagnostic plots, and visual predictive checks (VPCs).

Results: PK data were available from 23 individuals. Samples for determination of total antibody concentrations were taken prior to infusion, mid-infusion, end of infusion, and at 2, 4, 24, 72-120, 144-192, and 336 hours after the end of the infusion. Clearance decreased with increasing dose from the first to the third of six escalating dose levels before levelling, consistent with TMDD. The model-building process began with a TMDD model using FOCEI. A two-compartment TMDD model using quasi-equilibrium approximation (1) was tested, but was not adequate because the antibody plasma concentrations continued to rise for 2-4 hours after the end of the IV infusion in a majority of individuals. Therefore, a transit model was added to the TMDD model and tested with FOCEI. Due to problems with model minimization, covariance step failure, and protracted run times with FOCEI, the IMP method was tested, but the OFV increased with successive iterations. Therefore, the IMPMPAP method was implemented to test a series of 1 to 5 transit compartments. Compared to FOCEI, run times were shorter with IMPMPAP, and the model successfully minimized with covariance step completion. Finally, a model with infusion into a depot compartment and 4 transit compartments followed by a 2-compartment TMDD was selected that best fit the data.

Conclusions: The population PK model for this monoclonal antibody adequately described the data, and can be used for clinical trial dosing scenario simulations. This model, or sub-sections of the model, may also apply to other compounds administered by IV infusion that show a delayed t_{max}. Furthermore, the IMPMPAP estimation method offers a useful alternative to FOCEI for complex PK/PD models such as this TMDD model with depot and transit compartments.

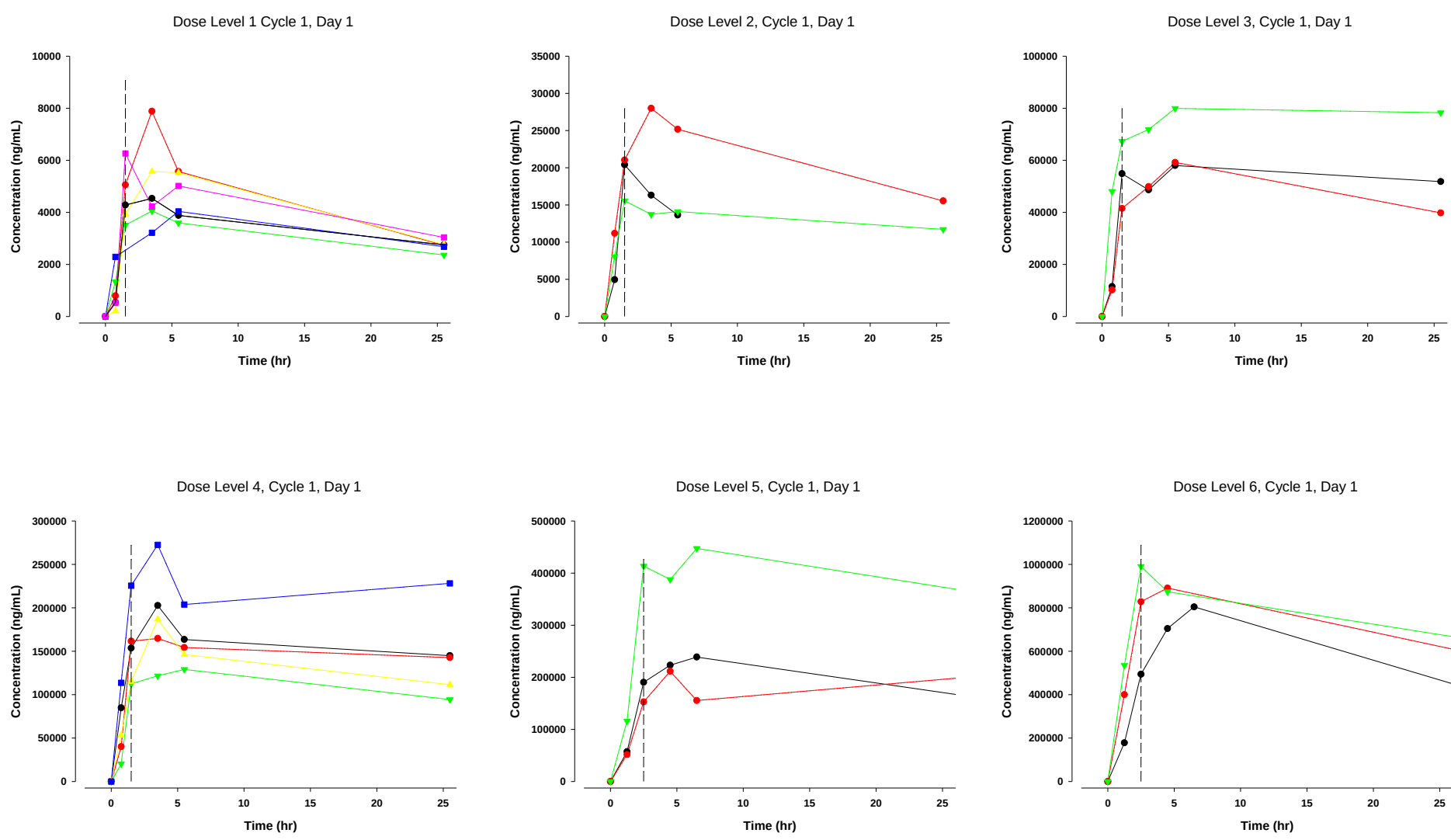


Figure 1. Individual concentration time profiles from 0 to 24 hours. Dashed vertical reference lines represent the end of the infusion (EOI). In most subjects antibody concentrations rise for 2-4 hours after the EOI across all dose levels.

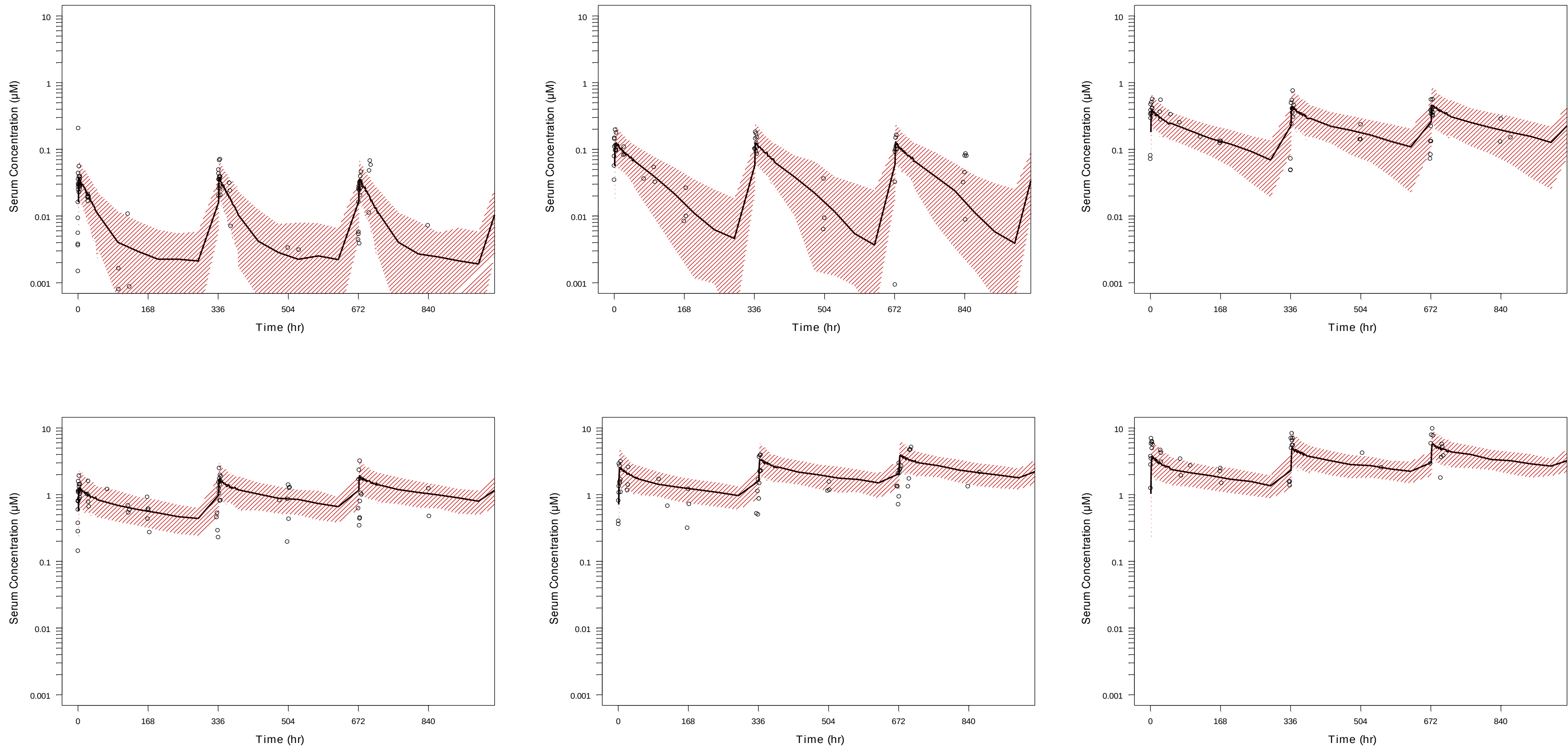
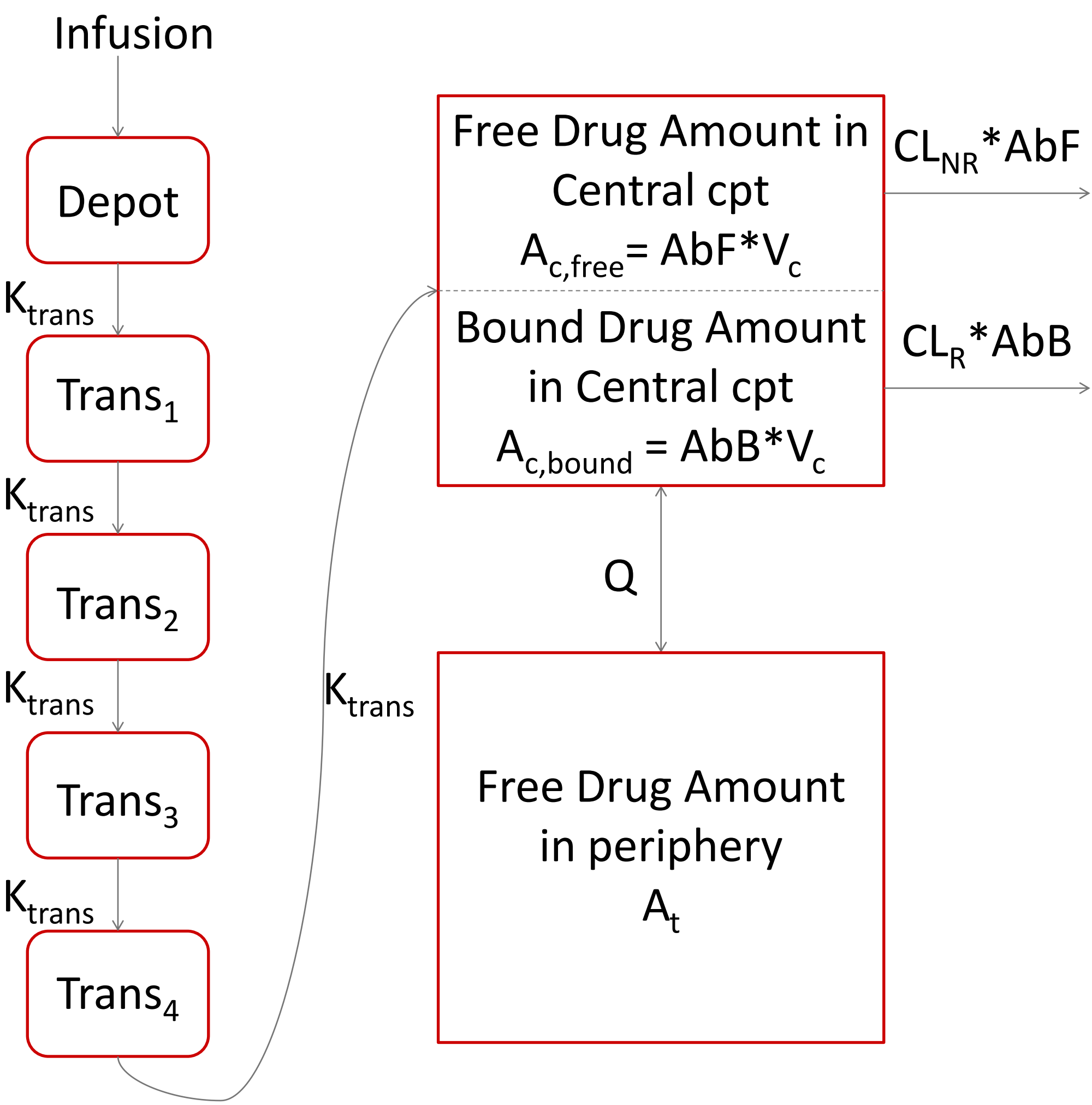


Figure 2. Visual predictive checks. Open circles are observed data. Solid black lines are median predictions. Hashed red areas are 90% prediction intervals.

RESULTS



$$MTT=5/K_{trans}$$

$$AbF = ((AbT-R_{tot}-K_D)+v((AbT-R_{tot}-K_D)^2 + 4*K_D*AbT))/2$$

Figure 1. Structural Model. The antibody is infused into a depot compartment and proceeds through four transit compartments ahead of the central compartment. The free antibody concentration is calculated based on the quasi-equilibrium approximation. MTT: mean transit time; K_{trans} : transit rate constant; AbT: total antibody concentration; AbF: free antibody concentration; AbB: bound antibody concentration; V_c : volume of the central compartment; R_{tot} : total receptor concentration; K_D : dissociation rate constant; CL_R : receptor mediated clearance; CL_{NR} : non-receptor mediated clearance.

Table 1. Modelling Process Highlights

Model	Estimation Method	Run Time (h) ^a	OFV ^b	Comments
1	FOCEI	5.5	-1799.851	Problems with minimization
2	IMP	4.8	381.737	OFV increased with each iteration
3	IMPMPAP	0.5	-1541.896	LBW on V1
4	IMPMPAP	2.5	-1819.409	Final Model no covariates on V1

^a All models were run on 4 nodes.

^b OFV was not used to discriminate between estimation methods. Rather OFV was one criterion used to discriminate between nested models run using the same estimation method.

Abbreviations: OFV: Objective function value; FOCEI: first order conditional estimation method with interaction; IMP: Monte Carlo importance sampling expectation maximization; IMPMPAP: IMP assisted by mode a posteriori estimation; LBW: lean body weight; V1: volume of the central compartment

METHODS

- ADVAN 13 TRANS 1 was used in NONMEM version 7.2.
- The final model was run using the IMPMAP estimation method with INTERACTION. The number of iterations (NITER) and number of individuals in each sample (ISAMPLE) were both set to 1000. Convergence testing was run on the objective function, THETAs, SIGMAs, and all elements of the OMEGA matrix (CTYPE=3). Ten iterations were used for convergence tests (CITER=10). The interval between iterations in convergence testing was 5 (CINTERVAL=5).
- Shrinkage was evaluated for ETAs and EPS
- Body size measures including height, weight, BSA, BMI, and LBW were tested as covariates on V1 according to the relationship
 $TVV1=THETA(1)*(Covariate/MEDIAN)**THETA(2)$
but none were significant enough to be retained in the final model.
- Inter-occasion variation was also tested on CL_R but was not significant in the final model.

Table 2. Parameter Estimates

Parameter	Estimate (%SEE)	IIV (%SEE)	Shrinkage (%)
V1 (L)	3.76 (12.3)	36.3 (24.3)	1.66
CL_R (L/h)	5.51 (9.89)	50.5 (26.9)	1.98
CL_{NR} (L/h)	0.00898 (7.24)	NE	
K_D (µM)	0.0089 (71.5)	NE	
R_T (µM)	0.000406 (28.6)	NE	
MTT (h)	0.27 (23.7)	64.2 (45.8)	19.5
V2 (L)	1.72 (14.4)	NE	
Q (L/hr)	0.038 (30.5)	NE	
Proportional Residual Error	20.7% (24.9)		4.82
Additive Residual Error (µM)	±0.00167 (169) (~0.24 µg/mL)		4.82

V1: volume of the central compartment; CL_R : receptor mediated clearance; CL_{NR} : non-receptor mediated clearance; K_D : dissociation constant; R_T : total receptor concentration; MTT: mean transit time; V2: volume of the peripheral compartment; SEE: standard error of the estimate; NE: not estimated

Discussion

- The quasi-equilibrium approximation (1) applies when the association and dissociation between the drug and the target are much more rapid than distribution and elimination of the antibody and the elimination of the antibody-target complex. This is assumed to be the case for the current model.
- A limitation of the current model is the lack of data on the receptor. Initial estimates for receptor related parameters (e.g., R_T) were based on pre-clinical species and literature values. Concentration time data for the target receptor have recently become available, and these information will be used to refine the model.

CONCLUSIONS

- The population PK model for this monoclonal antibody adequately described the data.
- This model can be used for clinical trial dosing scenario simulation.
- This model, or sub-sections of the model, may also apply to other compounds administered by IV infusion that show a delayed t_{max}.
- IMPMAP estimation offers a useful alternative to FOCEI for complex PK/PD models such as this TMDD model with depot and transit compartments.

Reference:

(1) Gibiansky L et al. J Pharmacokinet Pharmacodyn 2008; 35:573–591.