

INTRODUCTION

- MIT-001 is a potent mitochondrial-targeting antioxidant targeting various inflammatory diseases.
- Utilizing pharmacokinetic (PK), pharmacodynamic (PD), and safety data, we aimed to develop a population PK model for intravenous (IV) MIT-001 to provide an evidence for selection of appropriate doses in later trials.

MATERIAL AND METHODS

Data Source

- PK data from two phase 1 clinical trials with healthy male adults and two phase 2 clinical trials with patients were used (Table 1).
- PD data from the animal model was utilized.

Table 1. Detailed information on the pharmacokinetic data of each clinical study

	Study 1	Study 2	Study 3	Study 4
Population	Healthy	Patients	Healthy	Patients
Subject number	63	41	26	31
Treatment	0.3 – 200 mg IV infusion	1 – 10 mg IV infusion	3 – 30 mg IV multiple infusion	1 – 10 mg IV infusion
Sample number	1185	320	1038	242

Modeling Strategy

- The base model was developed including an evaluation of 1-, 2-, and 3-compartment models (NONMEM v 7.4.3)
- Various elimination models such as linear elimination, Michaelis-Menten kinetics, and elimination with autoinhibition were evaluated
- Covariate analysis included age, height, body weight, AST, ALT, serum creatinine, sex, and disease status (patient/healthy).
- Models were evaluated using objective function value, goodness of fit plots, visual predictive check, and bootstrap analysis.

Simulation

- The final model was used to simulate exposures for various doses (MIT-001 IV 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 mg twice weekly).
- Whether the PK profile after repeated IV infusion of MIT-001 was within the minimum effective dose observed in non-clinical study and maximum tolerable dose defined in the previous phase 1 clinical studies was identified.

RESULTS

Pharmacokinetic Modeling

- For improvement of the modeling process, log-transformed MIT-001 concentration with an additive residual error model was implemented.
- The 3-compartment model with autoinhibition effect best described the PK profile of MIT-001 (Figure 1).
- The disease status was a significant covariate on V1, and was included in the final model (Table 2).
- The GOF plots showed that the model-predicted concentrations were generally in agreement with the observed concentrations (Figure 2).

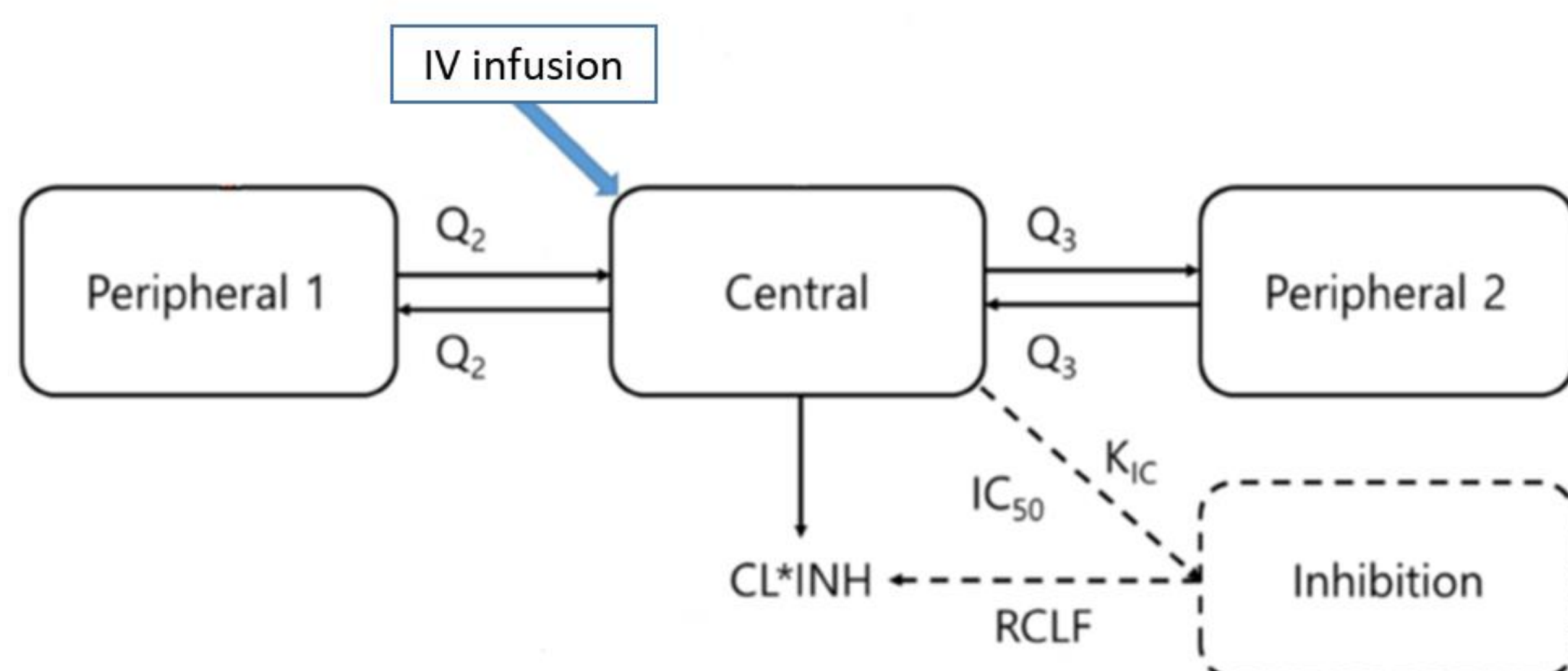


Figure 1. Structure of the population pharmacokinetic model of MIT-001

CL, Clearance; Q2 and Q3, inter-compartmental clearance, K_{ic}, rate constant into inhibition compartment; RCLF, remaining CL fraction; IC₅₀, concentration in the inhibition compartment yielding 50% of maximum clearance inhibition; INH, the inhibition fraction of CL

Simulation for Dose selection

- The simulated PK profile showed that about 80% of subjects were expected to reach effective exposure after twice weekly repeated dose of 20 mg for 5 weeks. More than 85% of subjects were expected to be tolerable at dose of 60 mg (Figure 3).

Table 2. Summary of parameter estimates for MIT-001 in the final pharmacokinetic model

Parameter	Estimates (RSE%)
Population parameter	
Central compartment volume (V1, L)	7.5 (9.5)
Effect of the subject status (patient/healthy)	4.7 (13.4)
Peripheral compartment volume (V2, L)	29.8 (9.9)
Peripheral compartment volume (V3, L)	59.9 (4.3)
Clearance (CL, L/h)	2.54 (4.3)
Inter-compartment clearance between compartment 1 and 2 (Q2, L/h)	108 (6.6)
Inter-compartment clearance between compartment 1 and 3 (Q3, L/h)	29.3 (10.2)
RCLF	0.667 (8.4)
IC50 (mg/L)	0.01
KIC (/h)	0.001 (57.9)
Inter-individual variability (IIV)	
IIV for V1 (%)	72.9 (7.4)
IIV for V2 (%)	88.2 (11)
IIV for CL (%)	37.9 (7.6)
IIV for Q2 (%)	36.3 (20)
IIV for RCLF (%)	27 (42.9)
Correlation between V1 and V2	-0.0563 (121.5)
Correlation between V1 and CL	0.0416 (56)
Correlation between V1 and Q2	0.137 (57.2)
Correlation between V2 and CL	0.115 (32.8)
Correlation between V2 and Q2	-0.0073 (965.8)
Correlation between CL and Q2	0.0505 (448.3)
Residual error	
Additive error	0.166 (5.4)

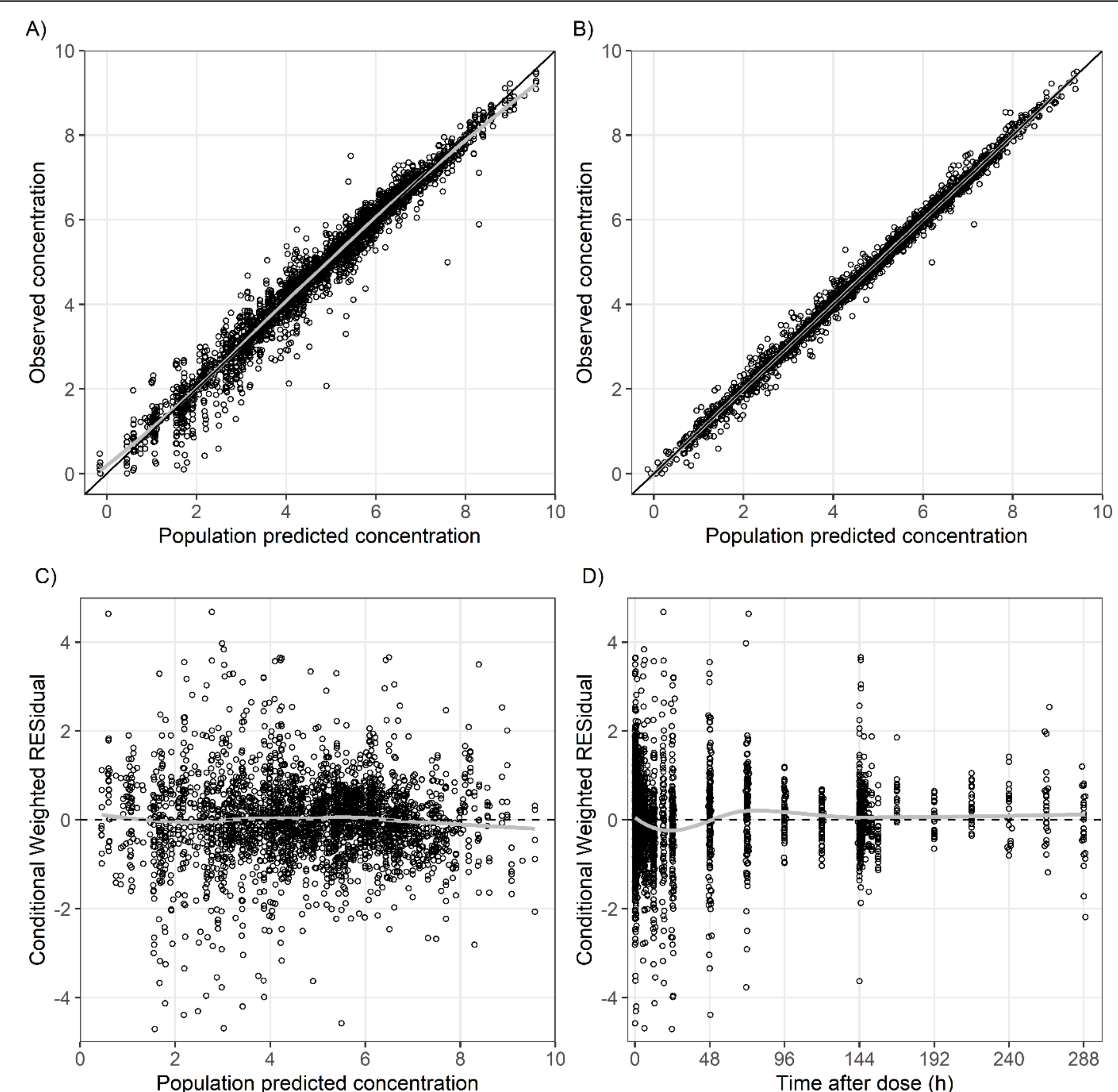


Figure 2. Goodness-of-fit plots of final population PK model of MIT-001

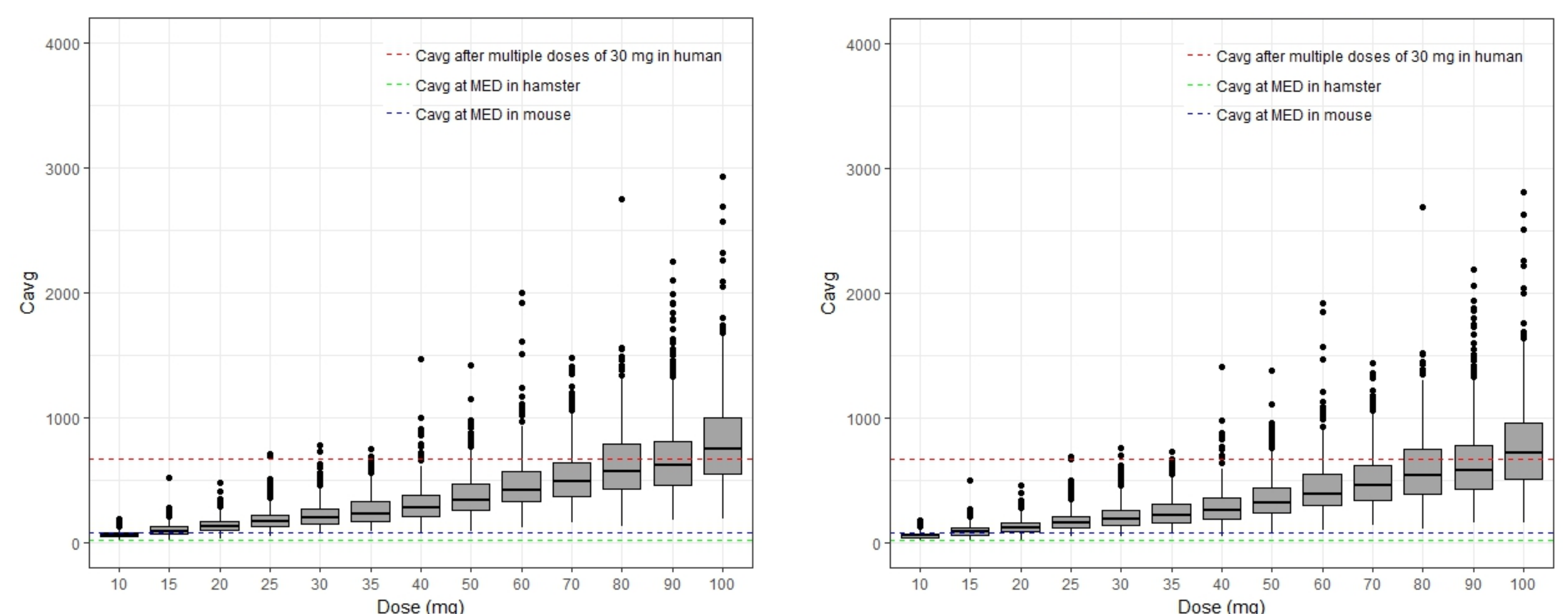


Figure 3. Predicted average concentration after twice weekly administration of MIT-001 on Week 5. Cavg, average concentration for dosing interval; MED, minimum effective dose

CONCLUSION

- Considering results of the non-clinical study and the previous clinical trials, the dose range of 20-60 mg is recommended for the following clinical trials.