

Clinical Trial Simulations Using a Pharmacokinetic/Enzyme-Occupancy/Pharmacodynamic Model of TAK-935, a Cholesterol 24S-Hydroxylase Inhibitor

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Introduction

TAK-935 is a potent and selective inhibitor of cholesterol 24-hydroxylase (CH24H), which converts brain cholesterol to 24S-hydroxycholesterol (24HC), a positive allosteric modulator at the N-methyl-D-aspartate (NMDA) receptor. 24HC can drive glutamatergic overactivation via NMDA channel activity, which implies a potential role in central nervous system diseases such as epilepsies. TAK-935 is currently under development for the treatment of patients with rare epilepsies.

Based on adult clinical data, a population pharmacokinetic (PK)/enzyme-occupancy (EO)/pharmacodynamics (PD) model was developed to provide an integrated understanding of the relationships between dose/exposure and brain EO or changes in plasma 24HC levels, as a PD measure. Using allometric scaling principles, this model was used to guide dose selection in adults (≥18 years old), adolescents (≥12 and <18 years old), and children (≥2 and <12 years old).

Methods

PK/PD Database

- A population PK (dose/exposure) model was developed to characterize the clinical PK profile of TAK-935 based on 4 phase I studies conducted in healthy adult volunteers (Table 1).
- Positron emission tomography (PET) data (study TAK-935-1003) were used to develop a PK/EO model to describe the relationship between TAK-935 exposure and target EO level.
- Individual 24HC plasma concentration data were used to describe the exposure-response relationship for the effect of TAK-935 on 24HC concentrations.

Overall, the PK/PD database consisted of 1727 PK measurements from 104 subjects and 2270 PD (24HC) measurements from 99 subjects, respectively. In addition, 20 EO observations from 11 individuals were available.

Table 1. Overview of Phase I Studies Included in the PK/PD Analysis Data Set

Protocol No.	Study Objectives	Study Design and Population	Dosage, Regimen, Route, Duration
TAK-935_101	Safety, tolerability, PK, and PD	Design: Phase I, randomized, double-blind, placebo-controlled, single rising dose Population: 48 healthy subjects aged 19 to 55 years, inclusive	TAK-935 15, 50, 200, 600, 900, and 1350 mg, single dose, oral solution, fasted condition
TAK-935-1002	Safety, tolerability, PK, and PD	Design: Phase I, randomized, double-blind, placebo-controlled, multiple rising dose Population: 40 healthy subjects aged 18 to 55 years, inclusive	TAK-935 100, 300, 400, and 600 mg qd and 300 mg bid, 10 or 14 days, oral solution, fasted condition
TAK-935-1003	Brain CH24H enzyme occupancy using the PET ligand [¹⁸ F]MNI-792 and PET imaging; relationship of occupancy to exposure	Design: Phase I, open-label, nonrandomized PET study Population: 11 healthy male adults aged 19 to 55 years, inclusive	TAK-935 50, 100, 200, 300, and 600 mg, single dose, oral solution, fasted condition [¹⁸ F]MNI-792, IV, up to 370 MBq (no more than 10 mCi), single dose, PET scan
TAK-935-1005	Relative bioavailability of tablet vs solution formulation; effect of food	Design: Phase I, randomized, open-label, 3-way crossover, single-dose Population: 9 healthy male and female subjects aged 18 to 55 years, inclusive	TAK-935 300 mg (as three 100-mg tablets), single oral dose under fed and fasted conditions; TAK-935 300 mg (solution), single oral dose, fasted condition

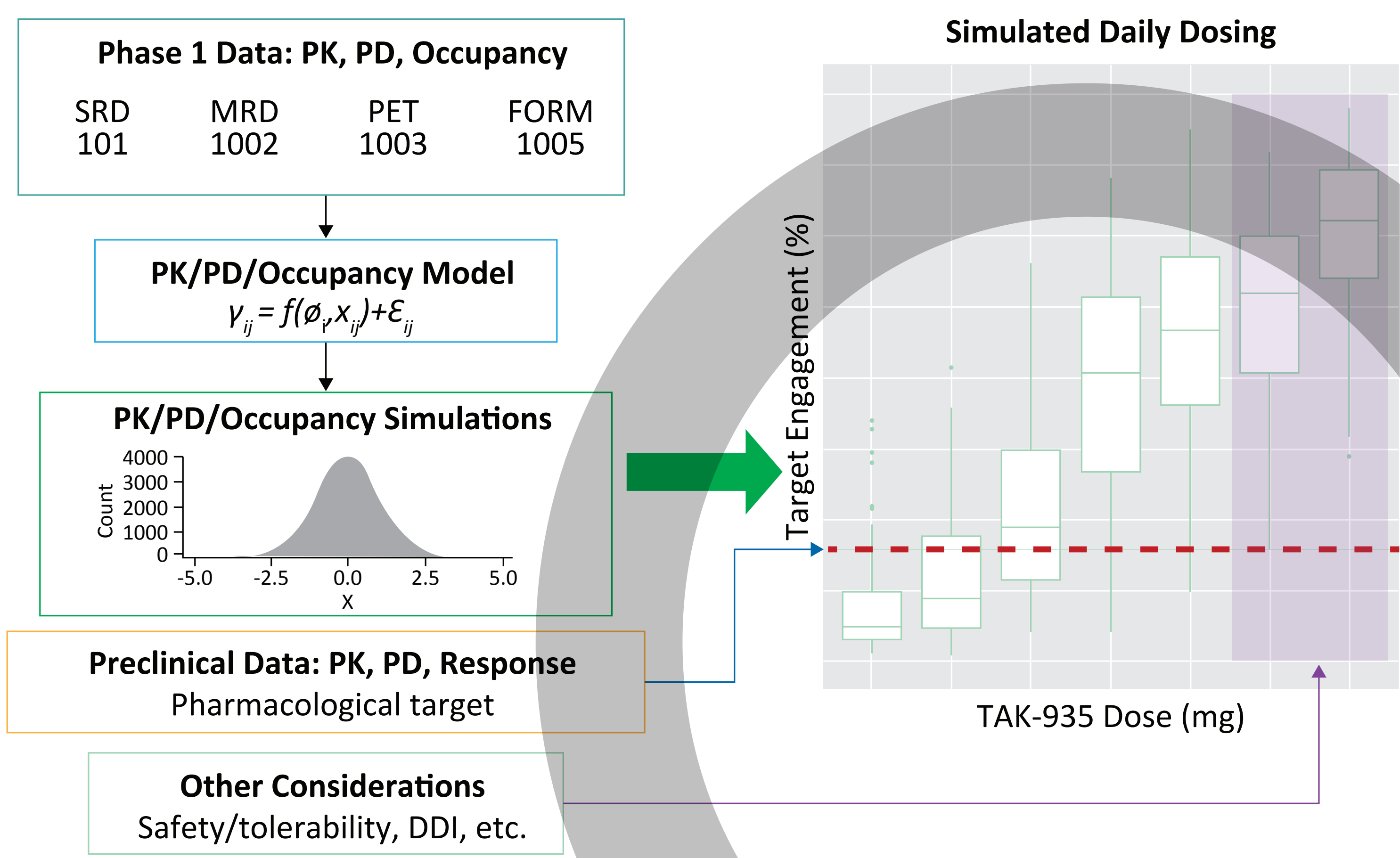
bid, twice daily; CH24H, cholesterol 24-hydroxylase; IV, intravenous; PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; qd, once daily.

PK/PD Model Development

A population PK/EO/PD model was developed to guide dose selection in adults (aged ≥18 years), adolescents (aged ≥12 and <18 years), and children (aged ≥2 and <12 years) (Figure 1). The model-based analysis was conducted using the first-order conditional estimation method with η-ε interaction in NONMEM 7 [1]. Analytical and simulation plots were constructed using R [2].

A rodent epilepsy model and preclinical EO data were used to define an efficacy threshold. With safety and tolerability data from healthy volunteers taken into account, a safe and potentially effective target dose range was selected.

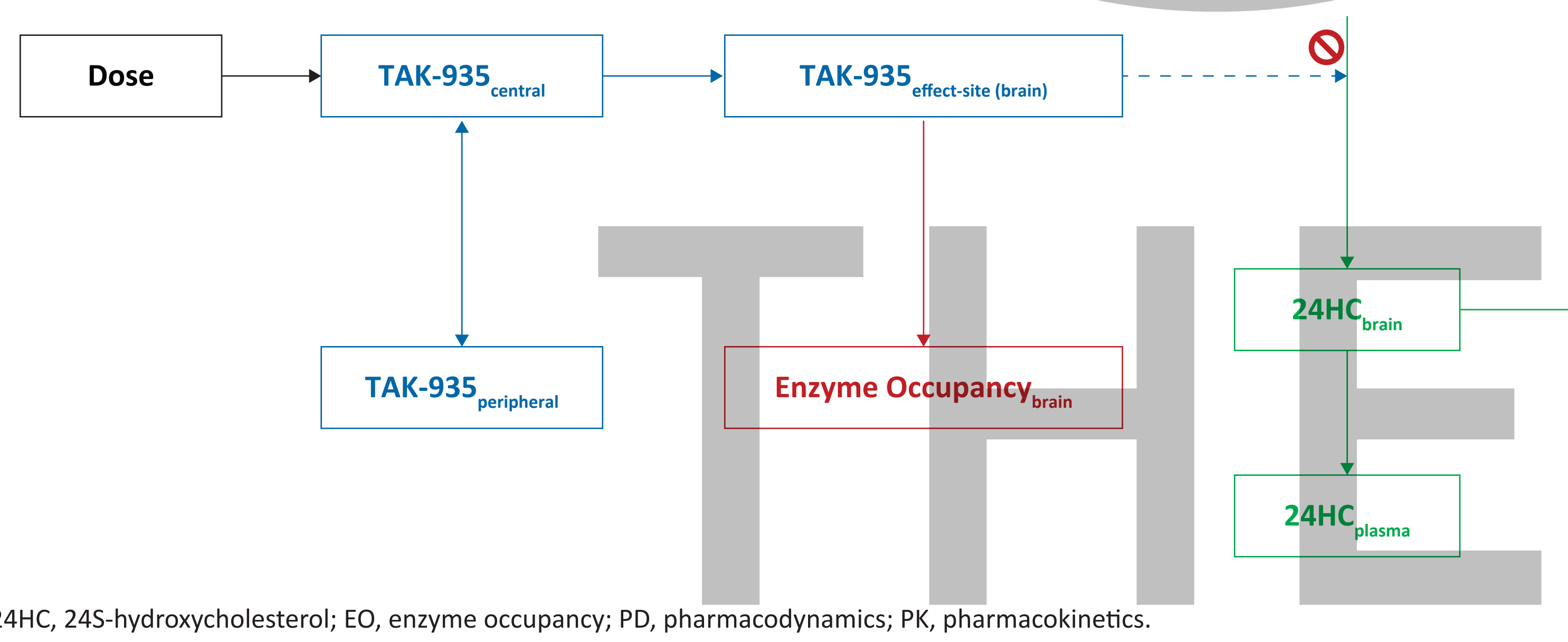
Figure 1. Dose Selection Based on Modeling and Simulation



FORM, bioavailability and food effect study; HV, healthy volunteers; MRD, multiple-rising-dose study; PD, pharmacodynamics; PET, positron emission tomography study; PK, pharmacokinetics; SRD, single-rising-dose study.

An overview of the PK/EO/PD models is depicted in Figure 2.

Figure 2. Overview of PK/EO/PD Relationships



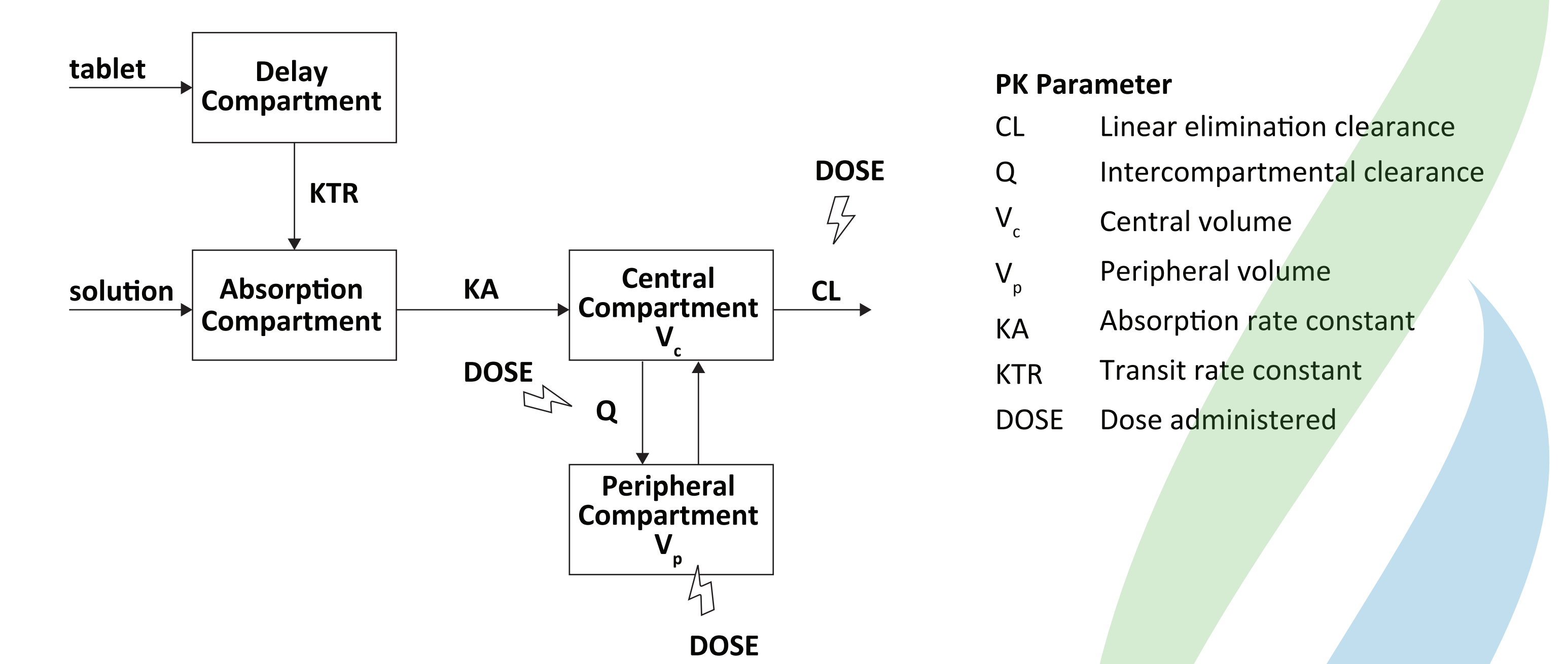
24HC, 24S-hydroxycholesterol; EO, enzyme occupancy; PD, pharmacodynamics; PK, pharmacokinetics.

Results

Population PK Model

As shown in Figure 3, a 2-compartment linear PK model with dose as a covariate on peripheral volume and distributional and elimination clearances adequately describes the complex PK profile of TAK-935. To accommodate the different dosing regimens (tablet, solution), additional transit compartments were introduced into the model to account for the observed delay in drug absorption. Selected PK model parameter estimates and their associated precision are listed in Table 2.

Figure 3. Schematic of Population PK Model



PK, pharmacokinetics.

Table 2. Selected Key Model Parameter Estimates of PK, PK/EO, and PK/PD Model

Parameter	Estimate	Standard Error ^a	Relative Standard Error (%)
KA (1/hr)	2.13	0.065	3.1
CL (L/hr)	203	10.2	5.0
V _c (L)	65.7	6.14	9.3
IIV on CL	0.124 ¹	0.026	21
IIV on V _c	0.313 ²	0.093	30
EC ₅₀ (ng/mL)	5.86	NA	22
IIV on EC ₅₀	0.229 ³	NA	39
IC ₅₀ (ng/mL)	5.44	NA	29

^aStandard error obtained from bootstrap analysis.

¹Corresponds to 90% prediction interval (PI): 2.7-12.9

²90% PI: 114-362

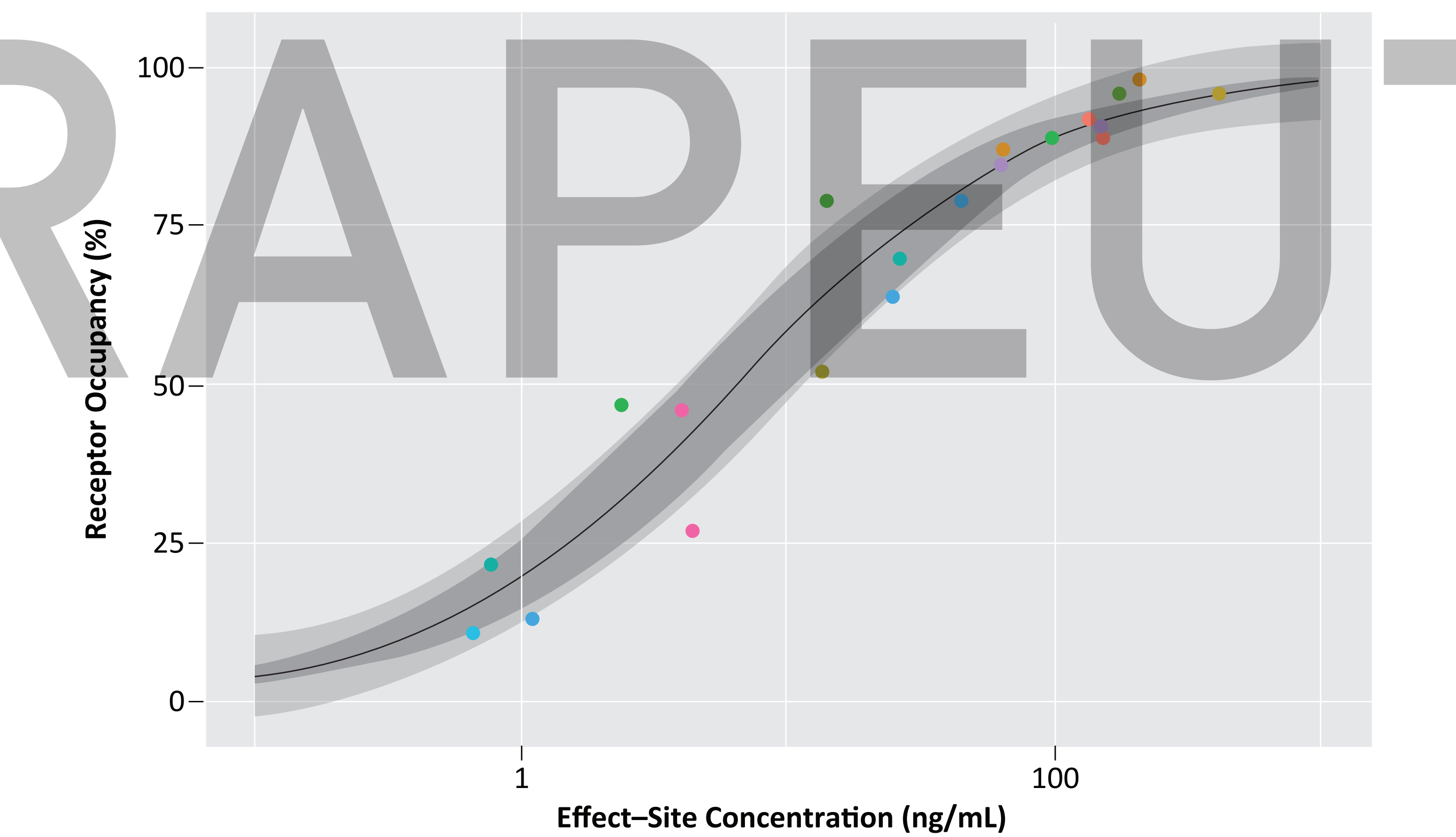
³90% PI: 26.2-165

CL, clearance of drug from plasma; EC₅₀, concentration of drug producing 50% of maximum effect; IC₅₀, concentration of drug producing 50% inhibition; IIV, interindividual variability; KA, absorption rate constant; NA, not available; PK, pharmacokinetics; PKEO, pharmacokinetics/enzyme occupancy; PKPD, pharmacokinetics/pharmacodynamics; V_c, central volume of distribution.

PK/EO Model

Results from a PET imaging study showed a time delay in the time course of plasma drug concentration and brain EO [3]. Therefore, an effect site compartment was added to the model to link individual predicted TAK-935 concentrations at the effect site to individual brain EO values. Figure 4 depicts the relationship between predicted and observed effect site concentrations and brain EO. It was assumed 100% of the tracer could be displaced from the binding site. An EC₅₀ of 5.86 ng/mL was estimated (Table 2).

Figure 4. Enzyme Occupancy vs TAK-935 Effect Site Concentration



Colored dots indicate observations; gray bands indicate model predictions: 95% prediction interval of individual prediction (dark gray) and simulated data (light gray, includes residual error).

PK/PD Model

A sequential modeling approach was used to describe the time course of 24HC in plasma. First, EO model parameters were fixed to estimates obtained from the PK/EO modeling step; then, predicted TAK-935 effect site concentrations were related to 24HC plasma concentrations using a semi-mechanistic inhibitory indirect response model, which resulted in an IC₅₀ of 5.44 ng/mL (Table 2).

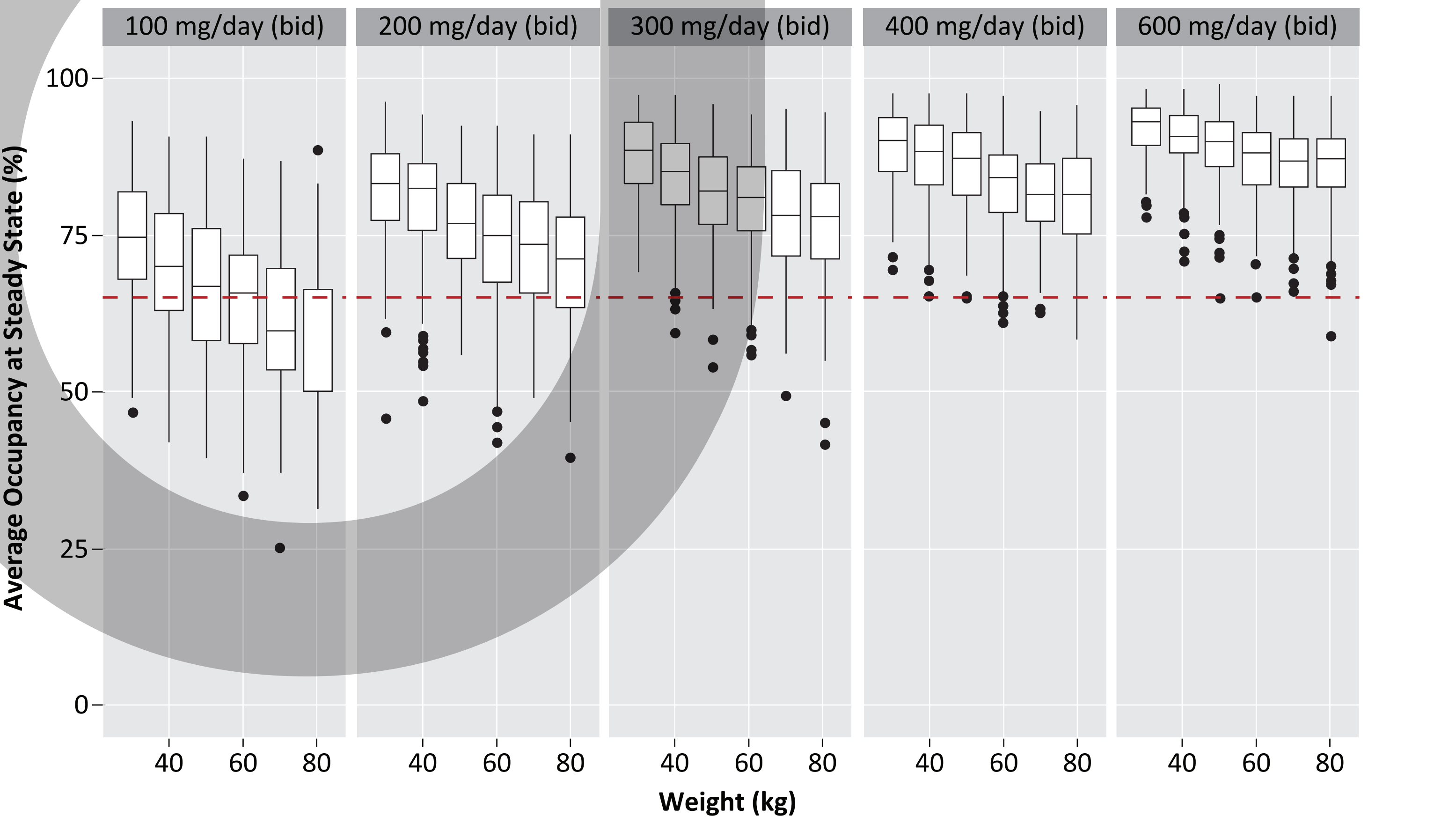
Simulation

The developed PK/EO/PD model was subsequently used to simulate TAK-935 plasma concentration, brain EO, and plasma 24HC concentrations at steady state for different dosing regimens in various pediatric subpopulations based on the following assumptions:

- To adjust for varying body weight across the age range of interest, the population PK model used allometric scaling of clearance and central volume of distribution, with fixed exponents of 0.75 and 1, respectively.
- Target expression levels in the brain are similar throughout the age range considered.
- Synthesis, metabolism, and distribution of 24HC are comparable for pediatric and adult subjects.

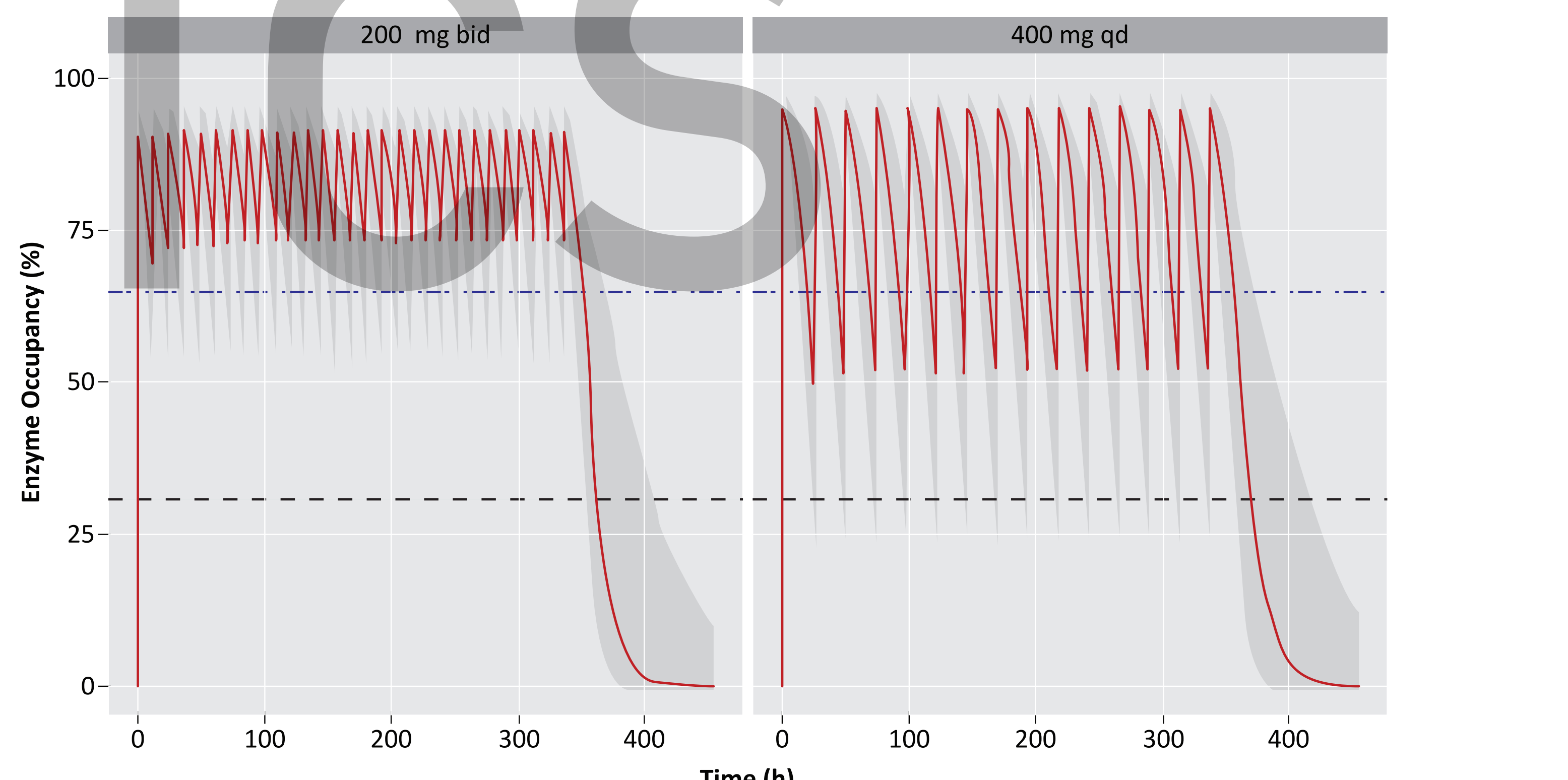
Enzyme occupancy (Figure 5, Figure 6) and reduction of PD Biomarker (24HC) in plasma were simulated for different daily doses of TAK-935 (tablet form) given once or twice daily (N=200 per scenario) for a weight range from 30 to 80 kg. Figure 6 shows simulated enzyme occupancy time profiles for a 70 kg subject.

Figure 5. Simulated Enzyme Occupancy at Steady State for Various Dose Regimens and Body Size



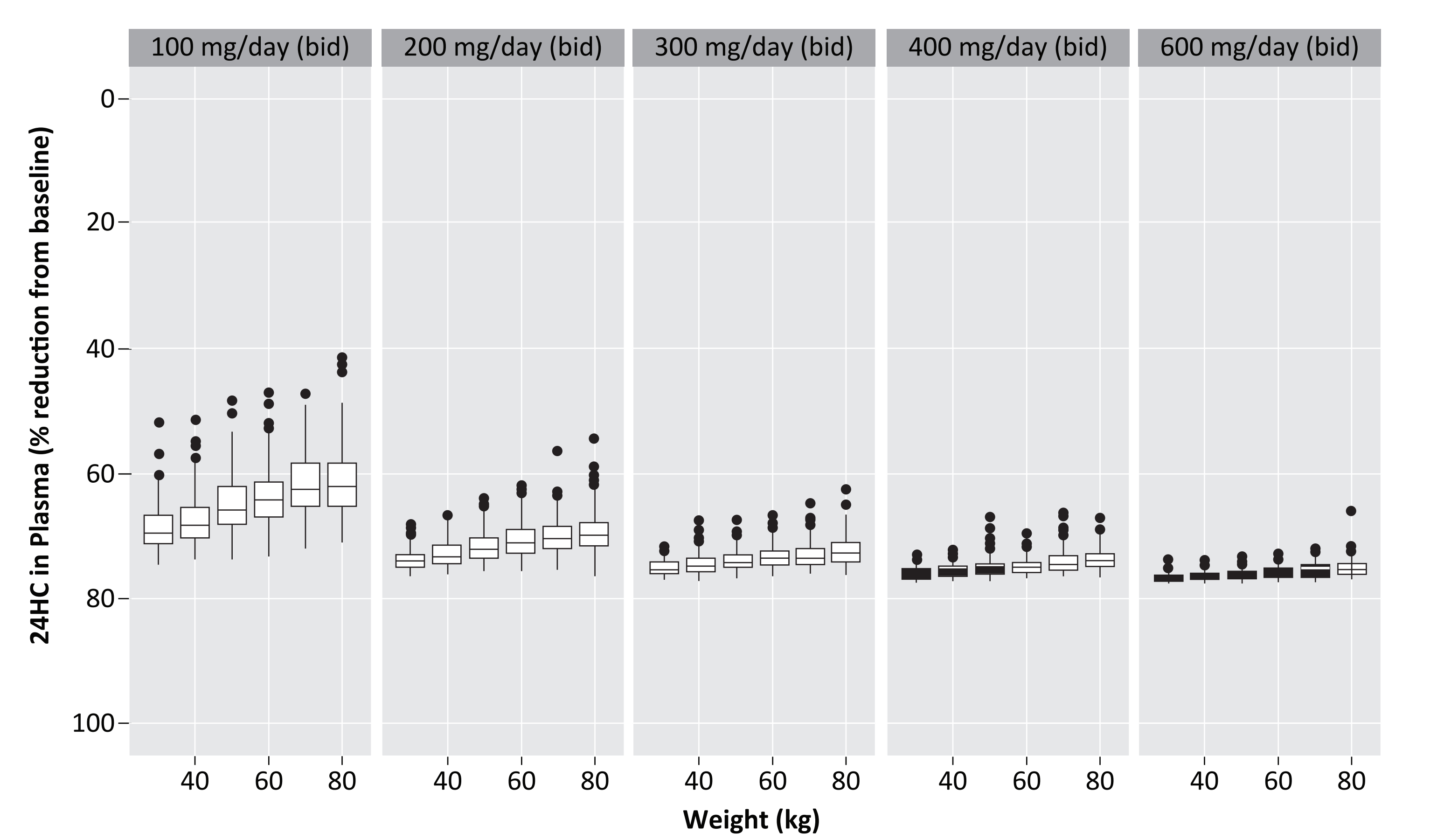
Reference threshold value of 65% shown in red, bid, twice daily.

Figure 6. Simulated Enzyme Occupancy Time Profiles



Median, red; 95% prediction interval, gray; reference values, blue (65%; average occupancy threshold) and black (30%; trough occupancy). bid, twice daily; qd, once daily.

Figure 7. Simulated Reduction of PD Biomarker (24HC) in Plasma for Different Doses (100-600 mg/day bid) and Weight Ranges From 30 to 80 kg



24HC, 24S-hydroxycholesterol; bid, twice daily; PD, pharmacodynamics.

Summary

- The PK/EO/PD model adequately described the relationships between observed TAK-935 plasma exposures, brain EO, and changes in plasma 24HC in adults.
- Model-based simulations suggested that doses ≥400 mg/day can provide sufficient target EO across the 30- to 80-kg weight range (Figure 5). In addition, twice-daily administration was superior to once-daily dosing, both with respect to target engagement above the prespecified threshold of 65% for efficacy based on preclinical information and to lower peak-to-trough fluctuations during the dosing interval (Figure 6). In addition, 24HC decreased by more than 60% from baseline (Figure 7).
- This model-based approach allowed integration of all pertinent PK and PD data using quantitative methods to guide selection of dose and regimen for optimal response in pediatric subjects while ensuring an acceptable safety and tolerability profile.

Acknowledgments

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