

Modeling and Simulation of Pharmacokinetics and H3 Receptor Occupancy for Dose Setting in a Phase IIa Study

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Objectives

AZD5213 is a histamine 3 (H3) autoreceptor antagonist currently under development for symptomatic treatment of Alzheimer's disease. Sleep disturbance is a well-known class-effect for H3 antagonists ⁽¹⁾ and is associated with high H3 receptor occupancy (RO) at night. Therefore the preferred time course of RO during a dosing interval would be high RO during day (for cognitive improvement) and low RO during night. The objective of this modeling and simulation activity was to investigate if it is possible to obtain large diurnal fluctuations in RO for AZD5213 as well as to suggest doses for a Phase II study that provide a wide spread in predicted diurnal RO vs. time-profiles.

Methods

Available data:

- Plasma concentrations from a multiple ascending dose (MAD) study in young and elderly healthy volunteers
- Plasma concentrations and H3 RO data from a human PET study in healthy volunteers

Following exploratory analysis of the PK data from a MAD study, a population pharmacokinetic model in NONMEM was developed.

To evaluate the stability of the final model parameters and the confidence intervals of the parameters, a bootstrap analysis using PsN was performed. Visual predictive checks were carried out for the final model using PsN. Due to the small number of individuals in each dose panel, the VPCs were prediction corrected ⁽²⁾.

The final population model was implemented in Berkeley Madonna. The model predicted plasma concentrations (C_p) were used together with the reported K_i-value, which is the drug concentration that yields an RO of 50 %, for H3 RO from the human PET-study (data on file, Figure 1) in order to calculate the anticipated RO vs. time profile using the formula:

$$RO(\%) = \frac{100 \times C_p}{K_i + C_p}$$

For each investigated dose, 1000 stochastic simulations of RO vs. time at steady state were carried out and the results were transferred to R for calculation of medians and 90% prediction intervals and plotting.

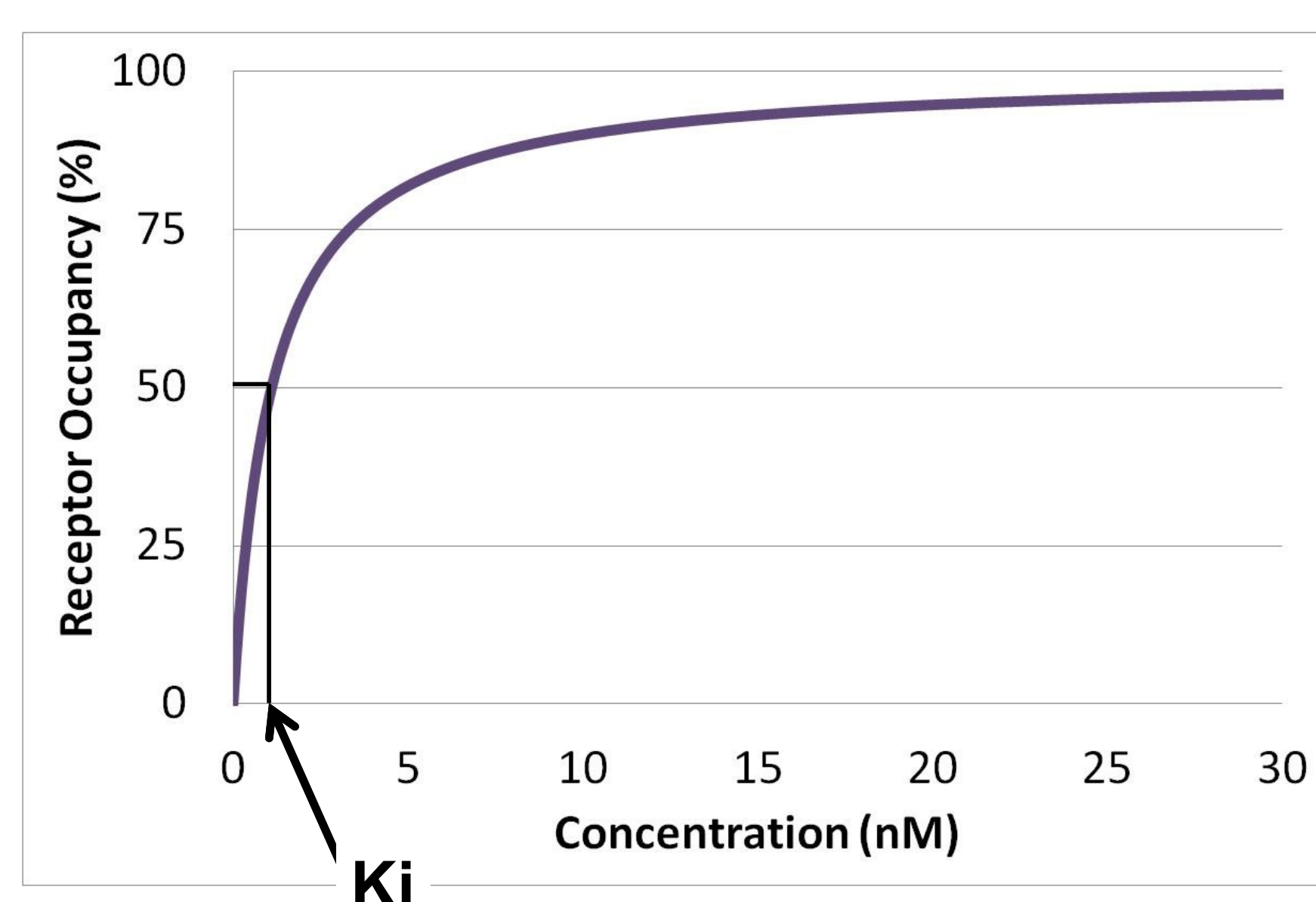


Figure 1 The K_i-value was obtained from a human PET study in healthy volunteers, data on file.

Results

A model that described the pharmacokinetics of AZD5213 in healthy volunteers was developed. A two-compartment model with 1st order absorption well described the PK of both young and elderly healthy volunteers after single as well as multiple dosing. The parameter estimates were stable in the bootstrap analysis. Figure 2 shows VPCs of the prediction corrected plasma concentration vs. time on log scale, stratified on the young and elderly panels. The VPCs show that the model well describes the data.

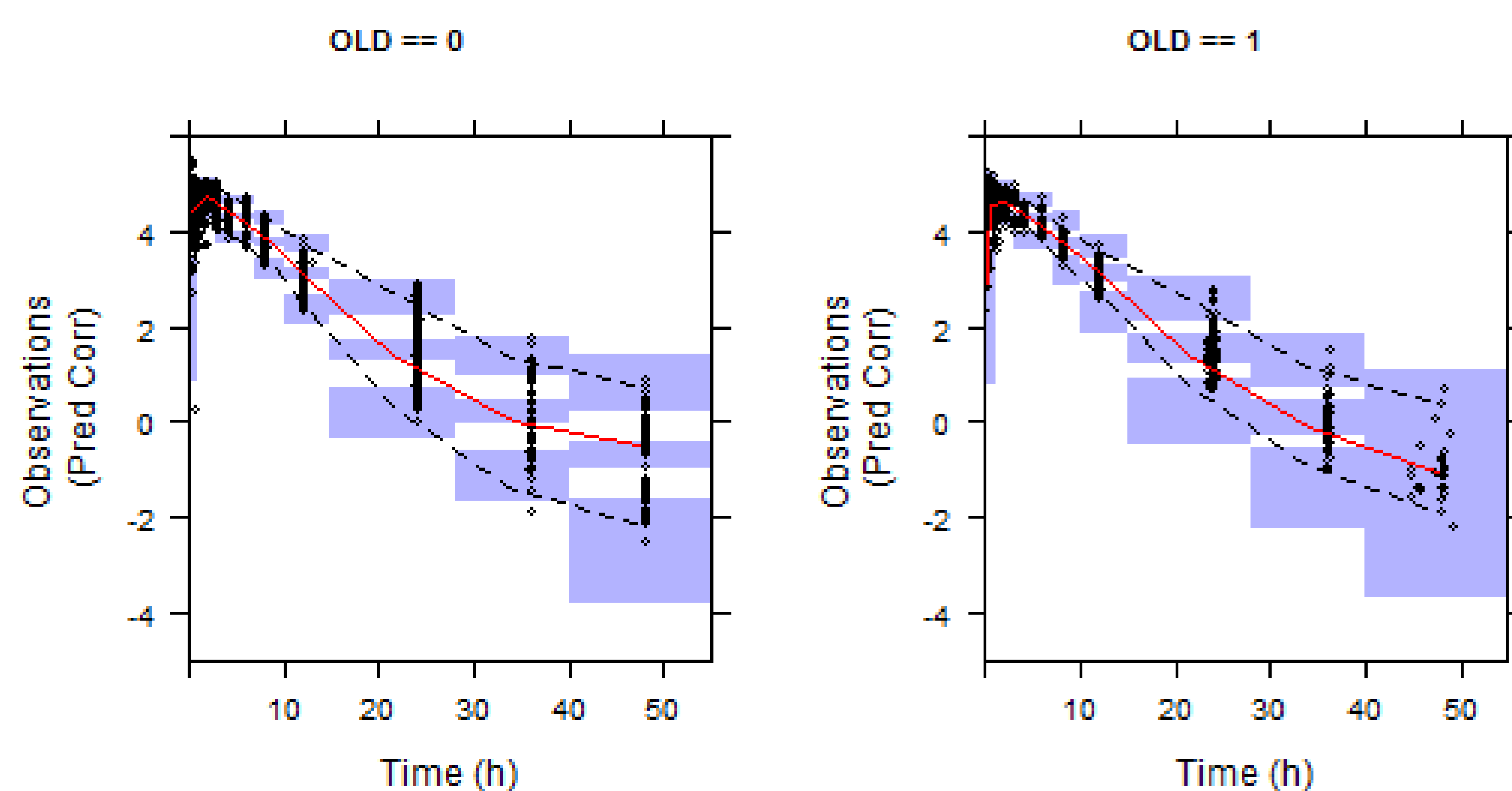


Figure 2 Prediction corrected VPCs stratified on the young (< 50 years) and elderly (65-80 years) panels. The observations are AZD5213 plasma concentrations on log scale.

Using simulations based on the popPK model and the K_i-value from the human PET study, the predicted RO vs. time profiles for a number of doses could be explored and doses with a wide range of fluctuations in RO over the dosing interval could be identified (Fig. 3). Inter-individual variability in the K_i-value could not be determined, therefore all variability in plots is attributed to the variability in PK. The selected doses were 0.5 mg, 2 mg and 6 mg. All doses yielded a maximum RO above 90%, and the RO 16 h later ranged between 45% to 90%.

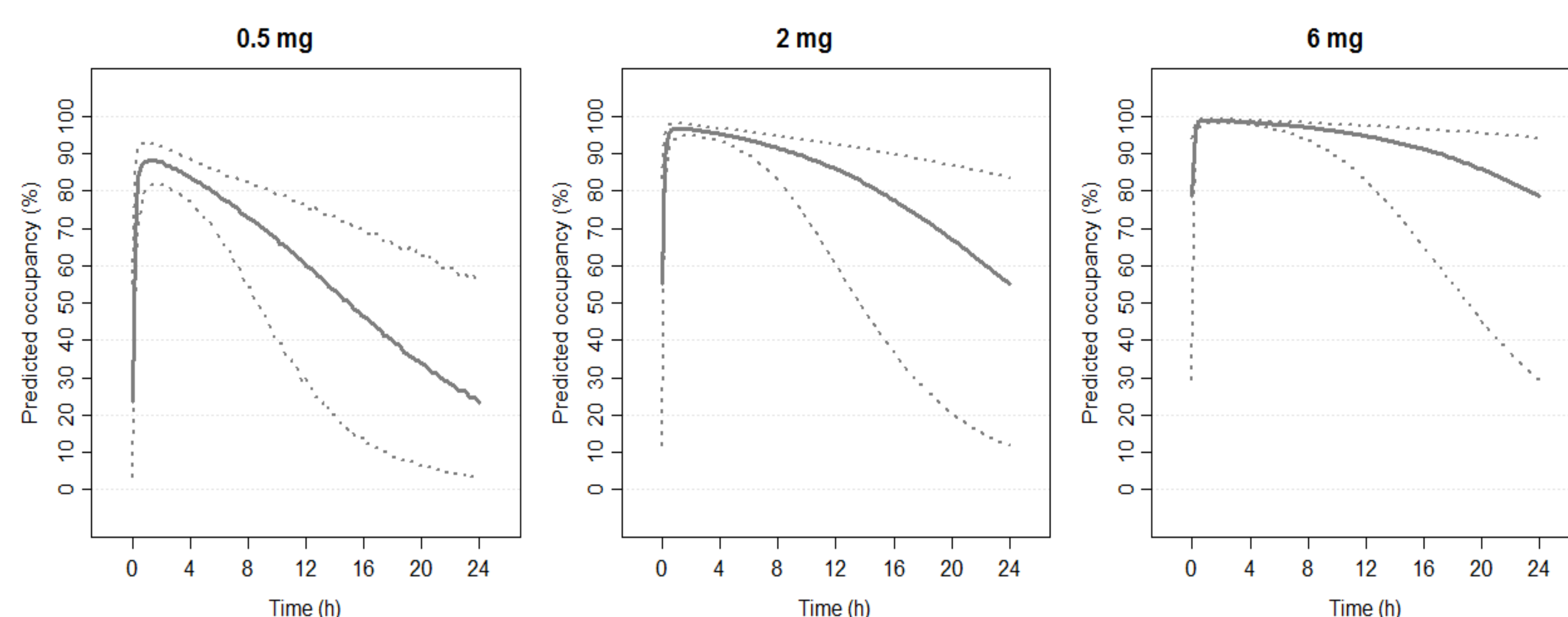


Figure 3 Receptor occupancy vs time profiles for AZD5213. Presented as median (solid line) and 90% prediction intervals (dotted lines).

Discussion and Conclusions

Using simulations based on the population PK model and the K_i-value from the human PET study, it was possible to identify doses with a wide range of RO vs. time profiles.

References

- [1] R. Parmentier et al. Biochem Pharmacol, 73 (2007), 1157– 1171.
- [2] M. Bergstrand et al. AAPS J, 13 (2011), 143-151.