

# Application of Physiologically Based Pharmacokinetic (PBPK) Modelling for Prediction of the Drug-Drug Interaction (DDI) Between Paroxetine and Terbinafine in a Japanese Population

## BACKGROUND

Paroxetine is an established perpetrator of DDIs and increases the exposure of drugs that are metabolised by cytochrome P450 2D6 (CYP2D6) following co-administration. Paroxetine is also metabolized by CYP2D6 and exhibits nonlinear kinetics during single and multiple dosing [1]. The nonlinear kinetics are more prominent in Caucasian extensive metabolisers (EMs) than poor metabolisers (PMs), mainly due to time-dependent auto-inhibition of the CYP2D6-mediated metabolism [2].

Although application of PBPK models can lead to successful prediction of DDIs, in some cases, it may not be possible, due to a lack of *in vitro* data or knowledge gaps in the models or that the ADME properties of the drug of interest have not been characterised fully. Thus, a “top-down” fitting approach can be combined with “bottom-up” extrapolation of all prior *in vitro* data to estimate the missing or “unknown” parameter. The model is then validated to ensure that inclusion of the “unknown” parameter allows recovery of the observed data. The refined model validated in a healthy population can be used to predict exposure or DDIs of the drug of interest in other ethnic groups or disease populations, accounting for differences in physiological parameters.

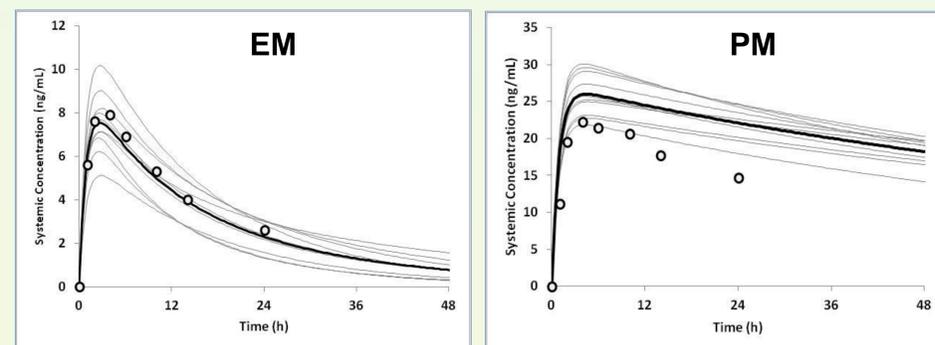
## AIMS

To develop a robust PBPK model that allows prediction of the exposure of paroxetine in healthy Caucasian EM and PM subjects.

To apply the model to predict a complex DDI between paroxetine (including auto-inhibition) and terbinafine (CYP2D6 inhibitor) in Japanese EMs accounting for differences in physiological parameters such as a lower CYP2D6 abundance (5 versus 8 pmol/mg protein).

## METHODS

Prior *in vitro* data for paroxetine reported by Jornil *et al.* [3] were incorporated into a PBPK model within the Simcyp Simulator (Version 12). Simulations of paroxetine were performed using the study design described by Sindrup *et al.* [1]. *In vitro-in vivo* extrapolation (IVIVE) of enzyme kinetic data for paroxetine was able to recover the observed clearance of paroxetine in Caucasian EMs but not PMs (Figure 1). Therefore, it was postulated that there may be an additional “unknown” metabolic route that had not been identified during assessment of *in vitro* activities.



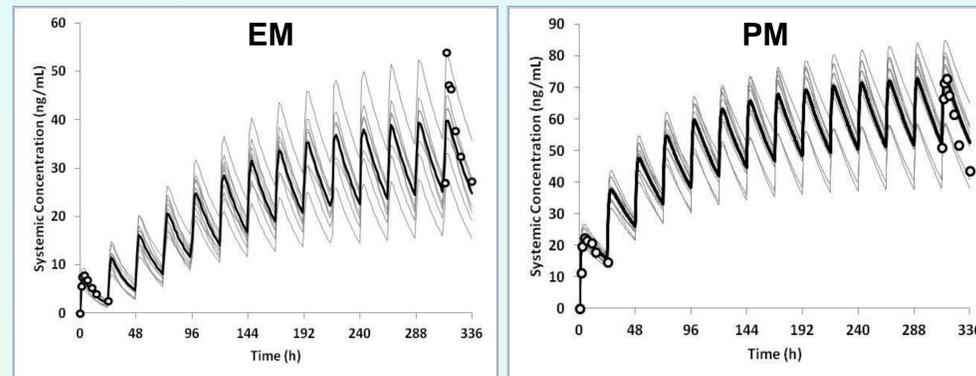
**Figure 1. Simulated (lines) and observed (circles; [1]) plasma concentration-time profiles of paroxetine after a single 30 mg oral dose in Caucasian EM and PM subjects.** The grey lines represent the outcomes of individual simulated trials (10 x 9) and the solid black line is the mean data for the population (n = 90).

## A. Model Development

A “top-down” fitting approach (*in vivo* concentration-time profile of paroxetine after a single oral dose in Caucasian PMs [1]) was combined with bottom-up extrapolation of all prior *in vitro* data for paroxetine within the Parameter Estimation module of the Simcyp Simulator. Optimisation was performed using the Nelder-Mead Minimisation Method and the Objective Function of the fit was determined using the Weighted Least Squares algorithm to obtain an estimate of 61.9  $\mu\text{l}/\text{min}/\text{mg}$  protein for the additional metabolic component in Caucasian PM subjects.

## B. Model Validation

Inclusion of the additional metabolic component of metabolism improved the model fit to *in vivo* data during multiple dosing of paroxetine in Caucasian EMs and PMs (Figure 2).



**Figure 2. Simulated (lines) and observed (circles; [1]) plasma concentration-time profiles of paroxetine after once daily oral dosing of 30 mg paroxetine in Caucasian EM and PM subjects.** The grey lines represent the outcomes of individual simulated trials (10 x 9) and the solid black line is the mean data for the population (n = 90).

## C. Model Application

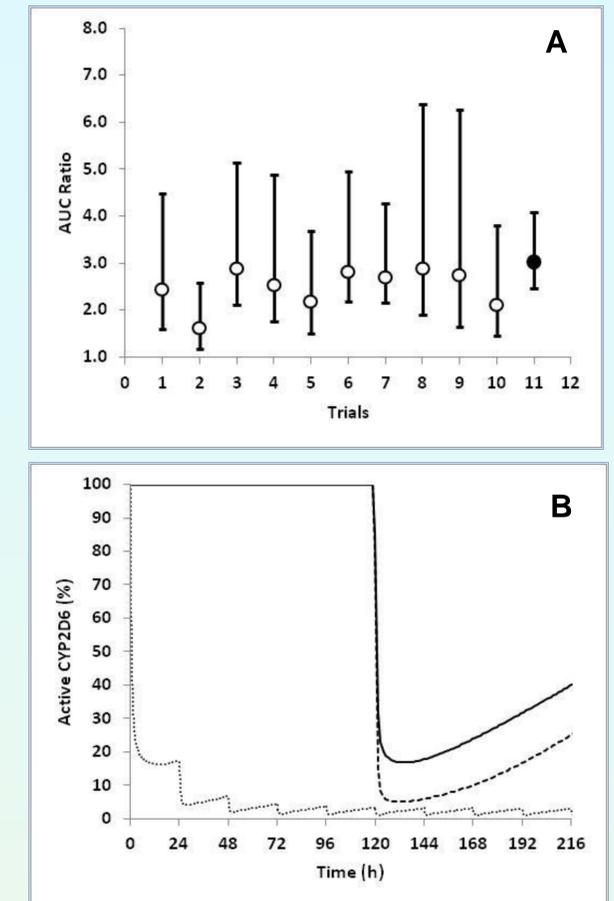
The “optimised” paroxetine model was then used to predict the DDI with terbinafine in Japanese EM subjects and compared with observed data [4]. System parameters for IVIVE in a Japanese population, such as those describing the demographic, anatomical and physiological variables (including enzyme abundance), were the same as those reported by Inoue *et al.* [5]. In addition to significant differences in CYP2D6 abundance, the frequency of CYP2D6 PM subjects is lower in a Japanese population (0.004 versus 0.082).

## RESULTS

The predicted increase in plasma  $\text{AUC}_{(0-\infty)}$  after a single oral dose of 20 mg paroxetine during co-administration of terbinafine (125 mg qd) in Japanese EM subjects was 2.6-fold (range for 10 virtual trials: 1.6 to 3.0-fold) which was reasonably consistent with the observed value of 3.0-fold. The variability across trials and in the clinical study is shown in Figure 3A.

Simulated profiles of active CYP2D6 in the liver indicate that 20% remains following administration of a single oral dose of 20 mg paroxetine but less than 5% is active after chronic dosing (Figure 3B).

Simulations of paroxetine and terbinafine during chronic administration of both drugs indicated the predicted AUC ratio was attenuated at steady state: it was found to be 1.08-fold (range for 10 virtual trials: 1.05 to 1.19-fold).



**Figure 3. A) Predicted median AUC ratios (95% confidence intervals) of paroxetine following a single oral dose of 20 mg in the absence of terbinafine and co-administered with terbinafine (125 mg q.d. for 6 days) in 10 different randomly selected trials of virtual Japanese subjects (n=12) and observed (solid circles) values [5]. B) Predicted profiles of active CYP2D6 remaining in the liver in the absence (solid black line) and presence (dashed line) of terbinafine.** The faint grey line indicates active CYP2D6 remaining during chronic dosing of paroxetine.

## CONCLUSIONS

Combining PBPK modelling with a fitting approach and reliable *in vitro* data, allowed accurate prediction of a complex DDI in a Japanese population.

Application of the validated model allowed other trial designs to be investigated, such as chronic dosing of both drugs. Although there were no *in vivo* data to confirm whether the prediction was correct, the fact that the paroxetine model was able to recover observed data for other scenarios may provide some confidence in the prospective DDI assessment.

## REFERENCES

- [1] Sindrup SH, Brosen K, Gram LF *et al.* *Clin. Pharmacol. Ther.* 51(3), 278-287 (1992).
- [2] Bertelsen KM, Venkatakrisnan K, Von Moltke LL, Obach RS, Greenblatt DJ. *Drug Metab. Dispos.* 31(3), 289-293 (2003).
- [3] Jornil J, Jensen KG, Larsen F, Linnet K. *Drug Metab. Dispos.* 38(3), 376-385 (2010).
- [4] Yasui-Furukori N, Saito M, Inoue Y *et al.* *Eur. J. Clin. Pharmacol.* 63(1), 51-56 (2007).
- [5] Inoue S, Howgate EM, Rowland-Yeo K *et al.* *Xenobiotica* 36(6), 499-513 (2006).