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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.

RESULTS
The predicted increase in plasma AUCparity after a single oral dose of 20 mg paroxetine during co-administration of terbinafine (125 mg q.d. for 6 days) 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).

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