

# Reduced PBPK model of dabigatran etexilate-dabigatran and its application for prediction of intestinal P-gp-mediated DDIs

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## Introduction

- Due to its high specificity and affinity for P-gp (efflux transporter), regulatory authorities have suggested to use dabigatran etexilate (DABE) as a clinical probe for the evaluation of intestinal P-gp mediated drug-drug interactions (DDIs) [1].
- Dose-dependent DDIs were reported for DABE with various P-gp inhibitors [2].
- The aims of this study were:
  - (i) to develop a reduced physiologically-based pharmacokinetic (PBPK) model for DABE (prodrug) and dabigatran (active metabolite)
  - (ii) to evaluate the model potential to predict dose-dependent P-gp mediated DDI risk.

## Methods

- A reduced PBPK model was first developed for dabigatran and optimised using clinical intravenous data collated from the literature. Dabigatran model included a peripheral compartment subdivided into two sub-compartments (i.e., intracellular and extracellular) to describe the slow distribution to non-eliminating tissues (Figure 1).
- Dabigatran model was linked to a reduced DABE model by the implementation of a mechanistic intestinal model; accounting for the heterogeneous distribution along the gastrointestinal tract and DABE hydrolysis into dabigatran. A single peripheral compartment was integrated to describe the non-eliminating tissues (Figure 1).
- Parameter optimisation was performed using a naive-pooled approach implemented in Nonmem v7.4.
- Model verification was achieved using clinical data collated from the literature (single and multiple dosing studies and a microdose DDI study with itraconazole (strong P-gp inhibitor)) (Figure 2).

## Results

- DABE-dabigatran PBPK model satisfactorily described DABE and dabigatran plasma concentrations following administration of DABE over a wide dose range (375µg-300mg) and different dosing schedules, alone and co-administered with itraconazole.
- PBPK model predicted successfully dose-dependent DDI with two other P-gp inhibitors (verapamil and clarithromycin) (Figure 3 and 4).

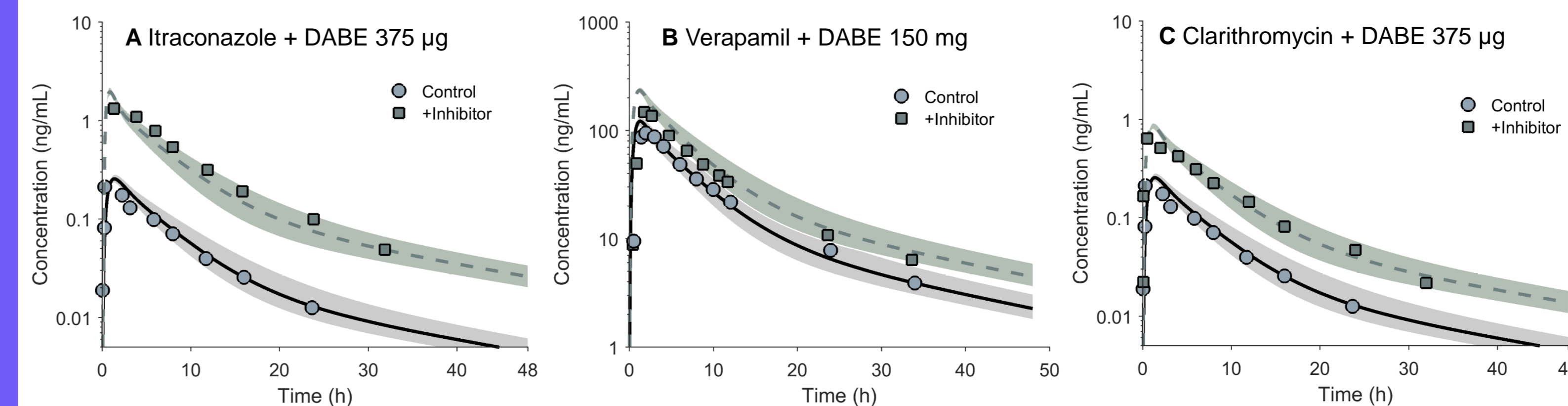


Figure 3. Dabigatran plasma concentration-time profiles in control and DDI conditions. Symbols represent mean observed dabigatran plasma concentrations, lines represent mean predicted and shaded areas are the 90% prediction intervals

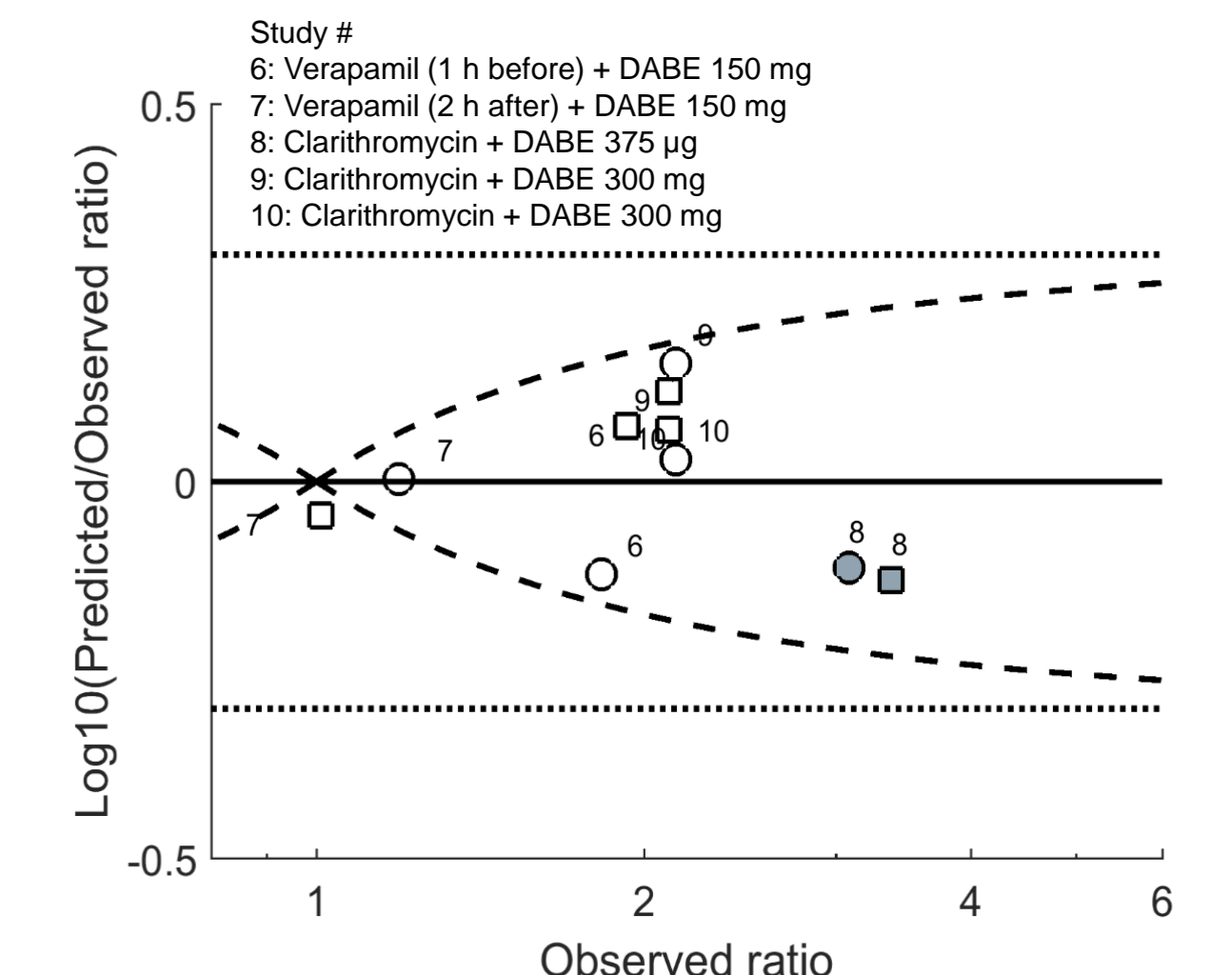


Figure 4. Predicted vs observed fold-change in AUCR (circle) and CmaxR (square)

- Simulated enterocytic concentrations allowed investigation of regional differences in intestinal P-gp inhibition and demonstrated a more pronounced P-gp inhibition at DABE microdose (375 µg) compared with DABE therapeutic dose (300 mg) (Figure 5).
- Dose staggering between itraconazole (solution) and DABE was also evaluated. Simulations of concomitant administration of itraconazole and DABE resulted in the highest DDI risk, whereas a 2-hour interval (after of before DABE) led to minimised DDI risk (Figure 6).

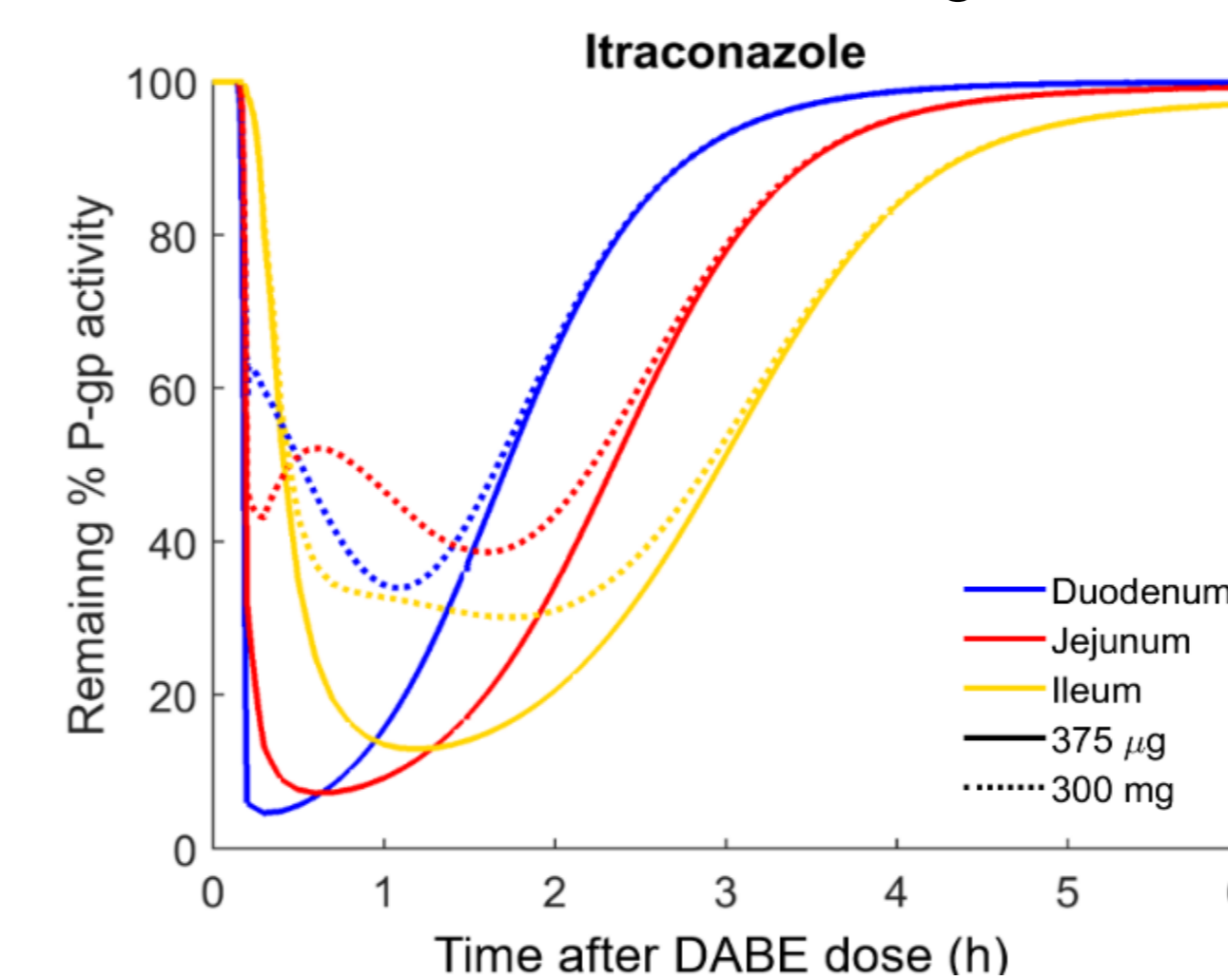


Figure 5. Simulated remaining percentage of P-gp activity in each intestinal segments following co-administration of itraconazole (solution) and a single oral DABE dose

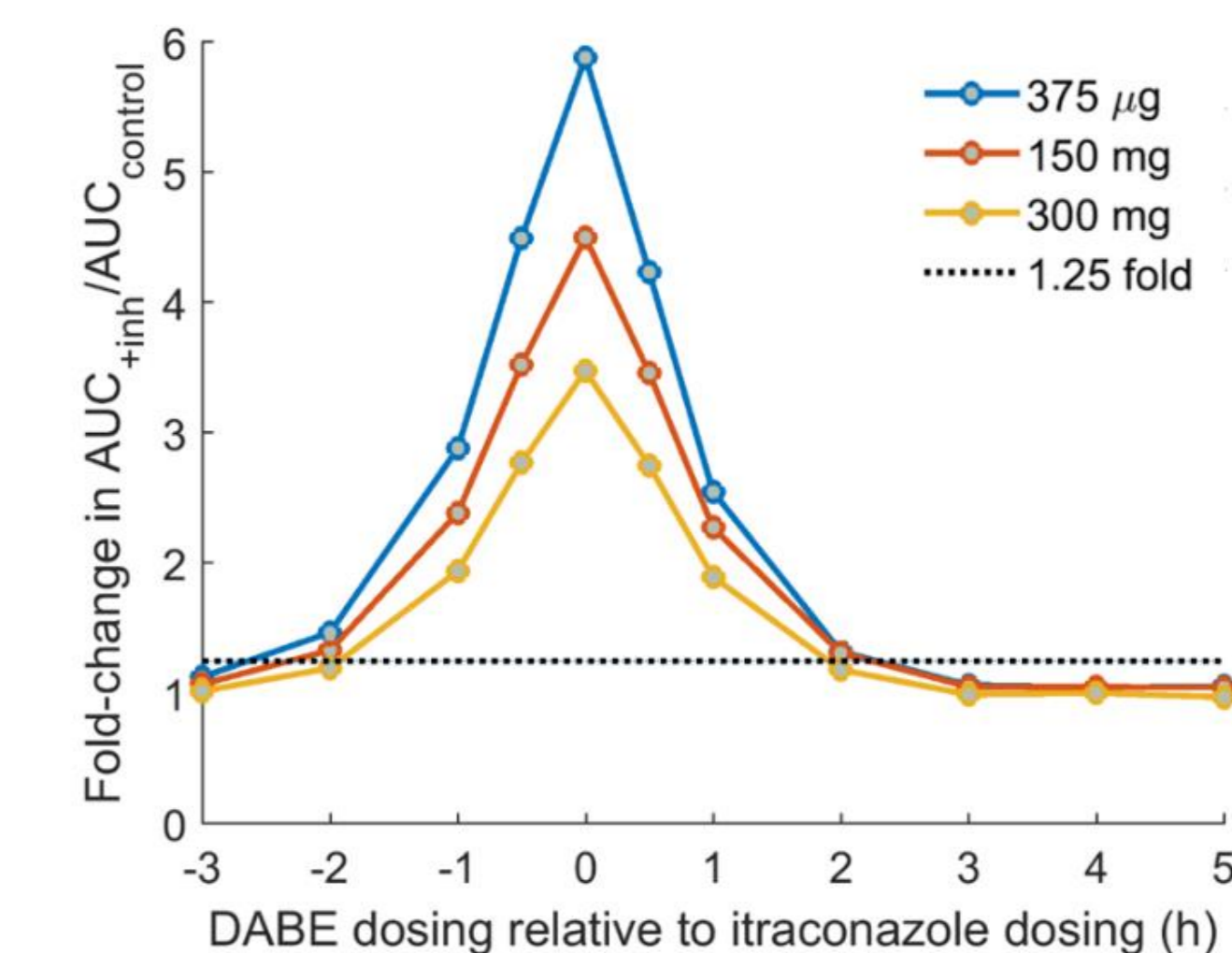


Figure 6. Effects of dose staggering of itraconazole (solution) and DABE doses on dabigatran P-gp DDI (AUCR)

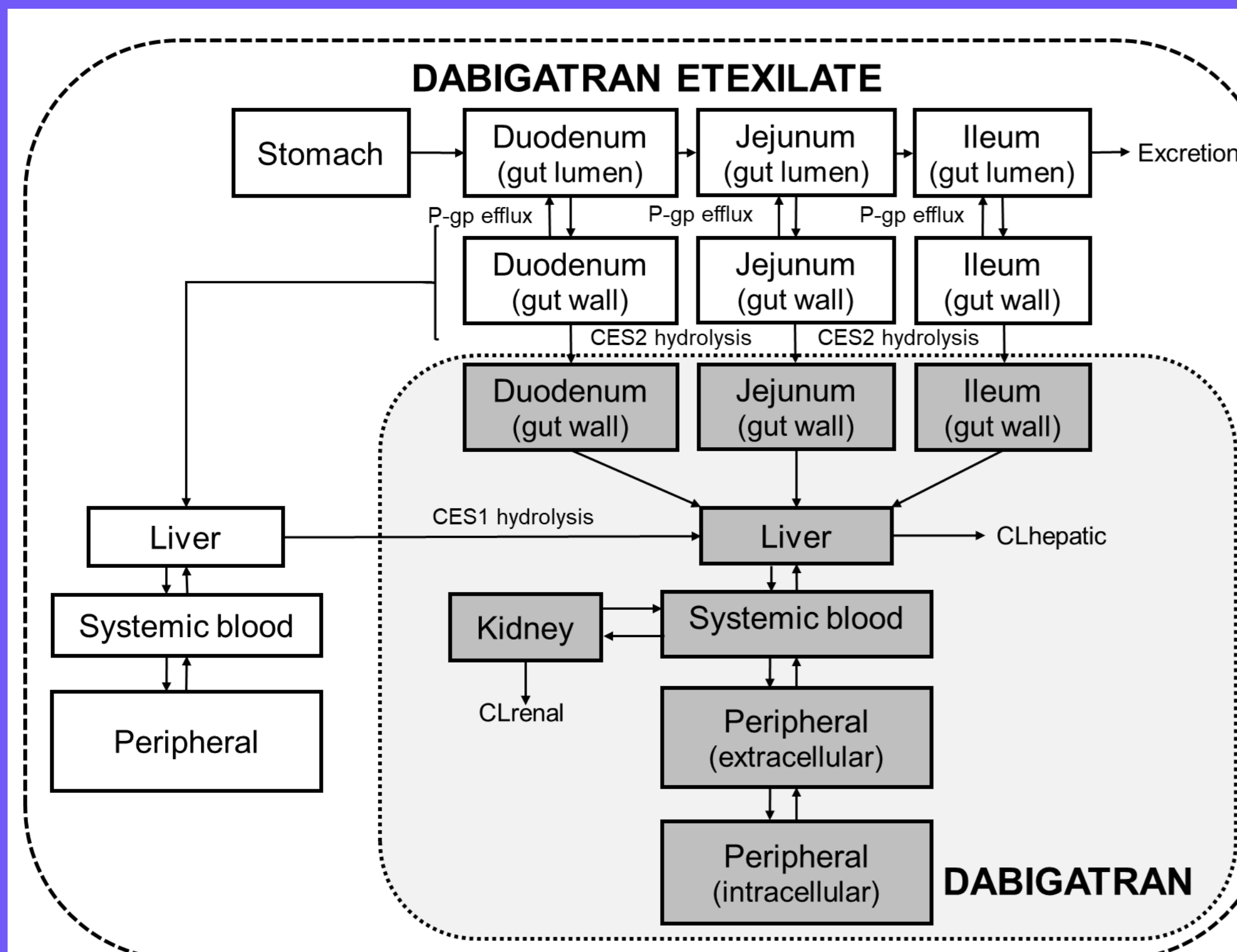


Figure 1. Schematic of dabigatran etexilate-dabigatran reduced PBPK model

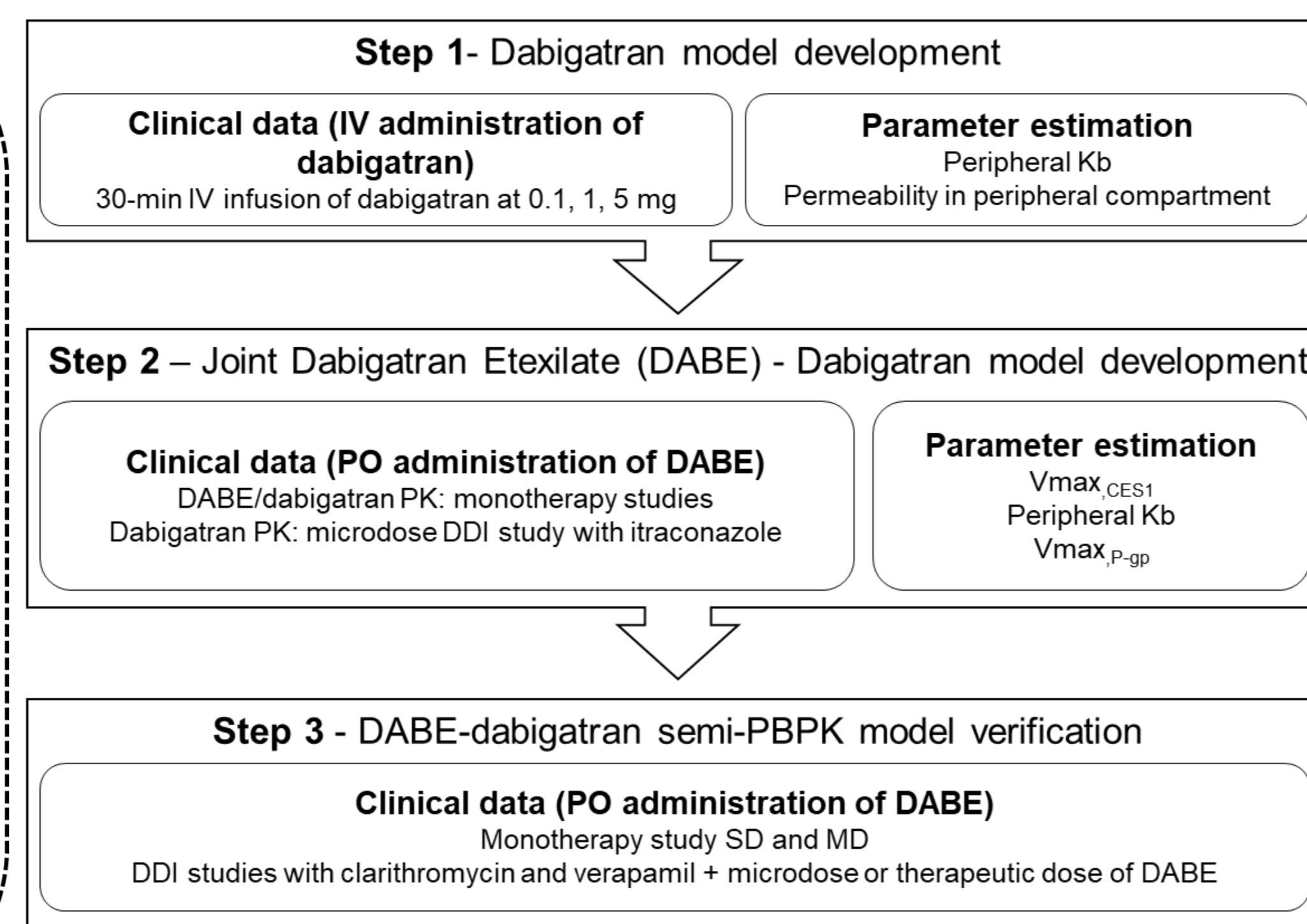


Figure 2. Workflow diagram for dabigatran etexilate-dabigatran reduced PBPK model development and verification

## Conclusions

- This modelling work is the first study to take into account dose-dependency in the evaluation of intestinal P-gp mediated DDI using a PBPK approach.
- The DABE-dabigatran PBPK model can be used to
  - inform the design of prospective clinical DDI studies with P-gp inhibitors
  - evaluate the minimum and/or maximum DDI risk via the simulation of dose staggering regimens
  - investigate intestinal regional differences.



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